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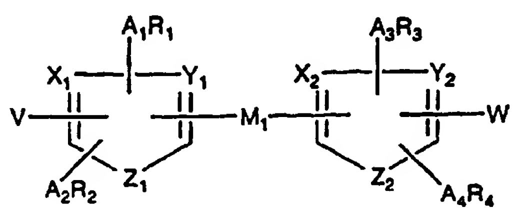

(I)

(57) Abstract

Methods for rapidly generating large rationally designed libraries of structurally-diverse small molecular weight compounds using a multicombinatorial approach. Also disclosed are compounds of formula (I).

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A METHOD FOR PREPARING AND SELECTING PHARMACEUTICALLY USEFUL NON-PEPTIDE COMPOUNDS FROM A STRUCTURALLY DIVERSE UNIVERSAL LIBRARY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of co-pending U.S. Patent Application Serial No. 08/101,074, filed August 3, 1993.

TECHNICAL FIELD

The invention relates to a method for preparing and selecting low molecular weight non-peptide compounds having desired pharmaceutical or other biological utility. More particularly, the invention is a method for preparing a structurally diverse library of low molecular weight compounds and then selecting from the library those compounds having the desired pharmacologic activity.

BACKGROUND INFORMATION

A key step in preparing and selecting pharmaceutically or other biologically useful compounds is identification of structurally-unique lead compounds. In 1990 it was estimated that nearly one-third of the $231 Million average cost for making a new therapeutic compound available for widespread public use was spent in identifying and optimizing a lead chemical structure. Traditionally and currently mass screening of large numbers of compounds and mixtures of compounds has been and is the most successful method for identifying chemical leads. Recent availability of robotic, rapid, high throughput biological screens is beginning to make possible efficient screening of hundreds of thousands of compounds per year.

Most screening libraries consist of a historical collection of compounds synthesized in the course of pharmaceutical research, natural products, and, more recently, peptide libraries. Each of these libraries has limitations. Historical pharmaceutical collections of synthesized compounds contain a limited number of diverse structures which represent only a small fraction of total structural diversity possibilities. Limitations of natural products libraries include the structural complexity of the leads identified and the difficulty of reducing these leads to useful pharmaceutical agents. Peptide libraries are limited to peptides or peptide mimics; to date conversion of peptide chemical leads into

pharmaceutically useful, orally active, non-peptide drug candidates in the absence of a small molecule chemical lead has been met with limited success.

Some of the peptide and peptide mimic libraries referred to above were prepared using combinatorial chemistry. The challenge facing medicinal chemists is to translate the success using combinatorial chemistry to prepare peptide and peptide-like compounds into technology suitable for efficiently preparing large libraries of low molecular weight non-peptide compounds. Solid phase chemistry for preparing low molecular weight compounds is desirable to effect such a translation. The following references are examples of the types of solid phase chemistry methods that may be useful in low molecular weight compound combinatorial chemistry.

In 1974, F. Camps et al. (Annales De Quimica 70, 848) reported solid phase synthesis of four related benzodiazepines. More recently Bunin and Ellman (J. Am. Chem. Soc. (1992) 114, 10997) and S. H. DeWitt et al. (PNAS (1993) 90, 6909) also reported preparation of a small number of benzodiazepines using solid phase chemistry. Two tetradecene-1-ol acetates also have been prepared on solid supports (C. C. Leznoff et al., Can. J. Chem. (1977) 55, 1143). Additionally, solid phase synthesis of 4,4'-stilbenecarbaldehyde has been reported (J. Y. Wong et al., Angew. Chem. Int. Ed. (1974) 13, 666).

The following references are examples of biphenyl and triphenyl compounds that have been prepared by well known synthetic organic chemical methods. A. A. Patchett et al. recently reported that certain biphenyl acylsulfonamides and biphenyl sulfonylcarbamates are orally active antagonists of the angiotensin II receptor (Medicinal Chemistry Abstract #80 (1993) ACS Meeting-Chicago). Other recently reported angiotensin II antagonists include several imidazopyridine and tetrazole-substituted biphenyl compounds (E. M. Naylor et al., Medicinal Chemistry Abstract #76 (1993) ACS Meeting-Chicago) and a series of carbon-tethered biphenyl pyrrole compounds (J. M. Hamby et al., Medicinal Chemistry Abstract #72 (1993) ACS Meeting-Chicago). Another recently reported substituted biphenyl angiotensin II receptor antagonist includes an exocyclic nitrogen link (A. S. Tasker et al., Medicinal Chemistry Abstract #338 (1993) ACS Meeting - Chicago). Others recently have reported that certain ortho-biphenylphenols are leukotriene antagonists (M. J. Sofia et al., Medicinal Chemistry Abstract #5 (1993) ACS Meeting-Chicago).

Preparation of various other substituted biphenyls has been reported. An example of the many references describing methoxy substituted biphenyls is M. G. Banwell et al. which describes certain trimethoxy and tetramethoxy biphenyls that have tubulin binding properties (CA118(19):191308u (1992)). Another such reference describes synthesis of several methoxy and ethoxy-substituted biphenyls for use in a peroxidase indicator system for basic media (CA118(1):3411a (1992)). 2,4',5-Trimethoxy-4-biphenylcarboxylic acid has been reported to have estrogenic activity (CA54:19584c (1959)).

Synthesis of 2,2',5,5'-(tetrapropynl-1-oxy)biphenyl has been reported without indication of its use (CA116(11):105745p (1991)). Similarly, 2,2',6,6'-tetrabenzyloxybenzyl has been reported (CA110(21):192346b (1988)) and 2,2',3,3'-tetramethoxymethylbiphenyl (CA97(11):91847y (1982)) have been reported without a suggested utility. Preparation of several trisubstituted and tetrasubstituted biphenyls and terphenyls has been reported (CA118(21):212566u (1993)).

Preparation of various substituted bis-[2,3-dihydroxyphenyl]methanes has been reported without an indication of their utility (Marsh et al., Ind. Eng. Chem. (1949) 41, 2176). Included in this reference is a description of synthesis of 2,3-dihydroxyphenyl-3',4'-dihydroxyphenylmethane. Preparation of substituted bisphenyl compounds having SO_2, S, CMe_2, or O moieties between the rings has been reported for use in making semipermeable composite membranes for liquid separation (CA109(18):151003y (1986)).

Thus, there remains a need for methods to efficiently prepare large libraries of low molecular weight non-peptide compounds and to select from such libraries compounds having desired pharmaceutical utility.

SUMMARY OF THE INVENTION

The presently invented method for preparing and selecting low molecular weight non-peptide compounds having desired pharmaceutical or other biological utility includes a system for rapidly generating large rationally designed libraries of structurally diverse small molecule compounds to explore multiparameter space that overcomes many of the disadvantages associated with using currently available libraries as a basis for identifying and selecting new pharmaceutical agents. The disclosed invention makes possible preparation of libraries of low molecular weight organic chemical compounds which have

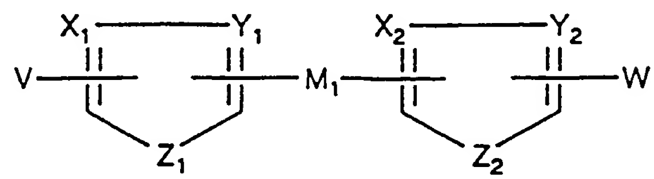
diverse chemical structures that are known and can be controlled. Additionally, other characteristics of the compounds that are important for pharmaceutical utility, such as solubility, can be controlled. Most importantly, however, because the compounds prepared using this invention are low molecular weight non-peptide compounds they are expected to be useful in a much broader spectrum of therapeutic applications than peptides which generally can only be administered by injection or inhalation.

DETAILED DESCRIPTION OF THE INVENTION

The presently invented method for preparing and selecting low molecular weight compounds having desired pharmaceutical or other biologic utility includes a multiple combinatorial approach to prepare structurally diverse libraries which contain biologically useful compounds. Combinatorial chemistry takes advantage of the nature of the interaction between biological ligates such as antibodies, receptors, enzymes, ion channels, and transcription factors, and their ligands such as antigens, hormones, neurotransmitters, and pharmaceutical agents. It generally is agreed that ligate/ligand affinity and interaction results from binding or interaction between at least three functional groups or chemical functionalities on the ligand and complementary sites on the ligate. Strong interactions between ligates and ligands are dependent upon the properties and three dimensional spacial orientation of the functional groups or chemical functionalities on the ligands. High affinity specific ligands for a given ligate have functional groups that: (1) bind tightly to the binding sites on the ligate and (2) are positioned to bring the functional groups into close proximity with the ligate binding sites in the biological milieu where the interactions occur.

Compounds prepared using the invented method have molecular weights of between about 200 and 1000 daltons, preferably between about 300 and 600 daltons, and contain two component parts: (1) scaffold moieties and (2) at least three functional groups. As used herein a "scaffold" is a molecule onto which functional groups can be attached in a manner that when two or more scaffold moieties are attached results in the desired spacial orientation of the functional groups. Scaffold moieties preferably are selected such that they can be prepared from available materials by known chemical reactions and readily allow for attachment of desired functional groups and/or other scaffold moieties in a variety of positions on the molecule. In this specification and claims, as indicated

by the context, "scaffold" may also refer to two or more attached scaffold moieties. Suitable scaffolds are compounds of the following formula:



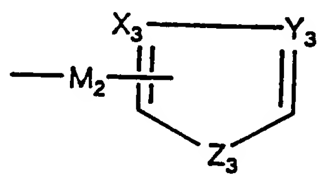
wherein:

M_1 and M_2 independently are a bond or CRR', CRR'CRR', CR=CR', or C≡C wherein R and R' independently are H or C_{1-6}alkyl;

X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

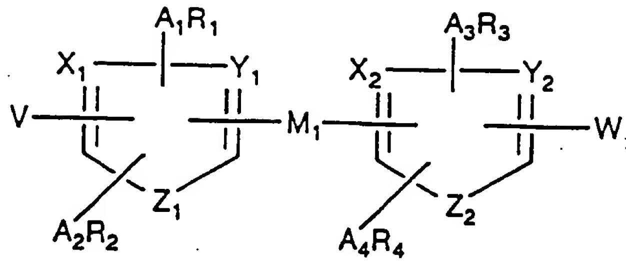
W is H or



X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH; and

V is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, or (C_{0-4}alkyl)NRR, or (C_{0-4}alkyl)CO_2R wherein each R independently is H or C_{1-6}alkyl.

Useful functional groups include the side chains of the 19 naturally occurring L-amino acids and the side chains of nucleotides found in nature. Additionally, non-naturally occurring mimics of these groups are useful. Preferred compounds of the invention which are prepared by combining preferred scaffold moieties with preferred functional groups are shown in Formula I below:



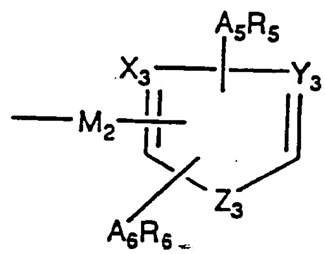
Formula I

wherein:

X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

W is H or



X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

M_1 and M_2 independently are a bond or $CR_{84}R_{85}$, $CR_{84}R_{85}CR_{84}R_{85}$, $CR_{84}=CR_{85}$, or $C\equiv C$;

V is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, (C_{0-4}alkyl)$NR_{22}R_{23}$, or (C_{0-4}alkyl)CO_2R_{76};

A_1, A_2, A_3, A_4, A_5, and A_6 independently are absent or present as O, S, NR_{60}; or C_{0-6}alkylC(O)NR_{21}, provided that at least three are present;

R_1, R_2, R_3, R_4, R_5 and R_6 independently are H, C_{0-6}alkylCOR_{15}, C_{1-6}alkyl$R_{16}R_{17}$, C_{1-6}alkylOR_{24} except methoxymethyl, C_{1-6}alkyl$NR_{25}R_{26}$, C_{0-6}alkyl$NR_{80}C(NR_{81})NR_{82}R_{83}$, C_{1-6}alkylindole, or C_{0-6}alkyl-D;

D is any one or multiple fused saturated or unsaturated five or six membered cyclic hydrocarbon or heterocyclic ring system containing one or more O, N, or S atoms that

are unsubstituted or substituted by any accessible combination of 1 to 4 substituents selected from C_{1-6}alkyl, NR_7R_8, OR_9, SR_{10}, or COR_{11}, halogen, CF_3;

R_7, R_8, R_9, R_{10}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{60}, R_{80}, R_{81}, R_{82}, R_{83}, R_{84} and R_{85} independently are H or C_{1-6}alkyl;

R_{12}, R_{13}, R_{14}, R_{16}, R_{17}, R_{18}, R_{24}, R_{25}, R_{26}, and R_{76} independently are H, C_{1-6}alkyl, phenyl, or substituted phenyl;

R_{11} is OR_{12} or $NR_{13}R_{14}$;

R_{15} is OR_{18} or $NR_{19}R_{20}$; or

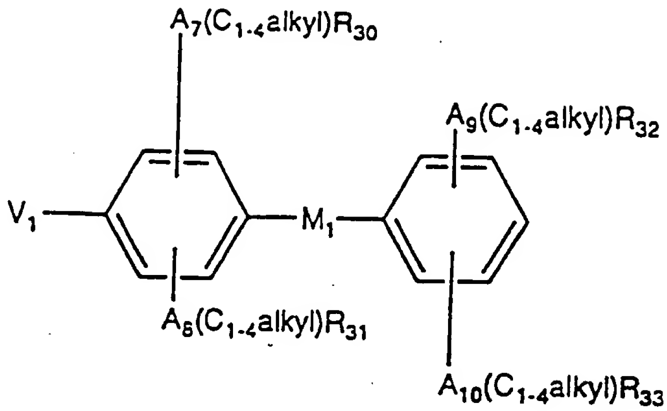
any pharmaceutically useful salt thereof except 2,2',5,5'-(tetrapropynl-1-oxy)biphenyl and salts thereof and compounds wherein at least three of A_1, A_2, A_3, A_4, A_5, and A_6 are oxygen and at least three of R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen, methyl, ethyl, or phenyl and salts thereof.

The compounds of Formula I constitute a universal library of compounds that includes pharmaceutically useful compounds.

As used in Formula I and elsewhere in this specification and the claims, "C_{x-y}alkyl" is a straight chain or branched, saturated or unsaturated alkyl group containing x to y carbon atoms wherein x and y are integers and "halo" includes bromo, chloro, fluoro, and iodo, and "substituted phenyl" is a phenyl group substituted by any accessible combination of halo, CF_3, OH, C_{1-6}alkyl, C_{1-6}alkoxy, COOH, $COOC_{1-6}$alkyl, NRR', or CONRR' wherein R and R' independently are H or $_{1-6}$alkyl.

In more preferred compounds of the invention X_1 to X_3, Y_1 to Y_3, and Z_1 to Z_3 are selected so that one or more of the ring systems is pyrrole, furan, thiophene, pyridine, pyrazole, pyrimidine, or isoxazole with phenyl being most preferred. Also in more preferred compounds of the invention D is one of the following ring systems substituted as described above: pyrrole, furan, imidazole, thiophene, pyridine, pyrazole, pyrimidine, pyridazine, or isoxazole with phenyl being most preferred.

More preferred compounds of the invention are shown in the following Formula II:



Formula II

wherein:

M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

V_1 is H, CH_3, OH, or CH_2OH;

A_7, A_8, A_9, and A_{10} independently are absent or present as O provided that three are O; and

R_{30}, R_{31}, R_{32}, and R_{33} independently are OH, NH_2, CO_2H, phenyl, substituted phenyl, $CONH_2$, $NR_{80}C(NR_{81})NR_{82}R_{83}$, C_{1-6}alkyl, imidazole, or indole wherein R_{80} to R_{83} are H or C_{1-4}alkyl.

Pharmaceutically useful salts of the above compounds include, for example, sodium, potassium, trialkyl ammonium, calcium, zinc, lithium, magnesium, aluminum, diethanolamine, ethylenediamine, megulmine, acetate, maleate, fumarate, lactate, oxalate, methansulfonate, ethanesulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate, phosphate, and nitrate. Other pharmaceutically useful salts are readily apparent to skilled medicinal chemists.

Some of the compounds included in Formula I can exist in more than one chiral form and thus exhibit stereoisomerism. Formula I includes all purified stereoisomers and racemic mixtures of the compounds within its scope.

In one aspect of the invention a preliminary step in preparing and selecting compounds having desired pharmaceutical or other biologic utility is preparation of a universal library. As stated above medicinal chemists and pharmacologists generally agree that interactions between biological ligates and ligands require that the ligand contain at least three functional groups in a spacial orientation that is complementary to the binding sites on the ligate. It also is known that the distance between the binding sites on ligates

is determined by the conformation of the ligate as it exists in its native environment and that effective ligands are those that have functional groups positioned to be complementary to such conformation. Because ligates are three dimensional in their natural setting, for any selected intramolecular distance between binding sites an essentially infinite number of possible specific positions for the binding sites exist. Thus there similarly is a very large number of possible functional group positions on the ligands that effectively interact with particular ligates. As used in this specification and claims a universal library is a collection of related small molecular weight compounds that with respect to spacial orientation of functional groups effectively samples a large segment of the possible specific positions within a selected distance and a sub-universal library is a universal library that is targeted to a particular biological ligate.

Preparation of bradykinin antagonists provides an example of the general approach to designing a sub-universal library. Bradykinin is a naturally-occurring nonapeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) that is formed enzymatically in the blood and extracellular fluids after injury.

At least two distinct receptor types, B1 and B2 appear to exist. Although activation of B2 receptors appears to underlie the most relevant biological actions of kinins, both B1 and B2 receptors could be important in developing therapeutic strategies. Bradykinin is a major pain producing substance that excites and sensitizes sensory nerves following trauma, burns, injury and infection. Peptide bradykinin antagonists block bradykinin-induced pain in animal models suggesting that a bradykinin antagonist would be effective for the treatment of a variety of painful disorders. Bradykinin has also been found in plasma exudates taken from the scalp of migraneurs and has been shown to cause severe vascular head pain upon intravenous injection suggesting that bradykinin antagonists would be useful for the treatment of headache. Bradykinin is a potent vasodilator of most peripheral arteries and also causes neurogenic inflammation by the peripheral release of substance P, neurokinin A, and CGRP from sensory nerve fibers. Bradykinin has also been found in fluid from arthritic joints. These results suggest that bradykinin antagonists might have an important role as antiinflammatory agents. Bradykinin has been proposed to play a role in the pathogenesis of asthma as well.

While an orally-active bradykinin antagonist is likely to be of immense therapeutic benefit, the potent bradykinin agonists and antagonists reported to date have been peptide

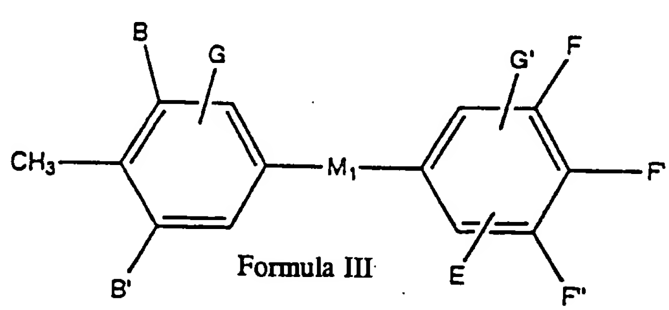
derivatives similar in size to bradykinin (which like bradykinin are expected to be rapidly degraded in body fluids).

Peptide analogs of bradykinin have shown that in general, replacement of Pro 7 with D-Phe or conformationally-constrained analogues as well as replacement of Phe 5 and 8 with thienylalanine or conformationally-constrained phenyl analogues affords competitive and selective antagonists of bradykinin. The C-terminal arginine is crucial for receptor activity. It appears that the N-terminal amino group is not necessary for activity since it can be acylated or removed without significant loss of activity. B1 selective antagonists are obtained by making the des-9 Arg analogues.

As an example, D-Arg^0-Hyp^3-Thi^5-D-Tic^7-Oic^8-bradykinin is a specific, potent, and long-lasting bradykinin antagonist being developed by Hoechst (Hoe-140) for allergic rhinitis and asthma.

Furthermore, Kyle et al. have incorporated unnatural amino acids in the C-terminus of bradykinin which introduce ß-turn stability and conclude that a ß-turn in the four C-terminal amino acid residues might be a prerequisite for high receptor affinity (D. J. Kyle et al., J. Med. Chem. (1991) 34 (3): 1230-33).

Using the information described above it is possible to design a sub-universal library that is likely to possess bradykinin antagonist activity. The ß-turn likely at the C-terminal portion of bradykinin suggests that the peptide antagonists are not fully extended at the receptor and likely occupy a distance of 10 -18Å. This is an ideal size to be mimicked by a bisphenyl scaffold and the size, shape, and group variations are explored by preparing a large library of compounds guided, or limited, by previously reported SAR studies on bradykinin receptor antagonists. This approach can be carried over to B_1 receptors by leaving out the arginine mimic on the A-ring. Using the previously described SAR data on bradykinin peptide antagonists the following compounds of Formula III are expected to include bradykinin antagonists:



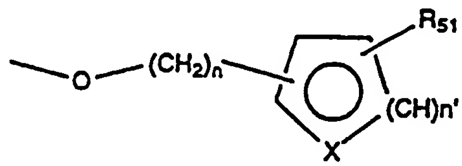
Formula III

wherein:

M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

B and B' are H, $O(CH_2)_nNR_{40}C(NR_{41})NR_{42}R_{61}$, or $O(CH_2)_{n'}NR_{43}R_{44}$ wherein R_{40}, R_{41}, R_{42}, R_{43}, R_{44} and R_{61} independently are H or C_{1-3}alkyl, n and n' are 2 or 3; provided one of B and B' is H;

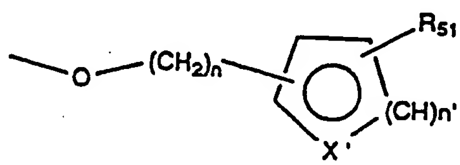
E is



wherein X is CH, N, NH, O, or S; n is 1-3; and n' is 1 or 2;

F, F', and F'' are H, $O(CH_2)_nNR_{45}C(NR_{46})NR_{47}R_{62}$, or $O(CH_2)_{n'}NR_{48}R_{49}$ wherein R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, and R_{62} independently are H or C_{1-3}alkyl, and n and n' are 2 or 3; provided two of F, F', and F'' are H;

G and G' are H, $O(CH_2)_nOR_{50}$, or



wherein X' is CH, N, NH, O, or S;

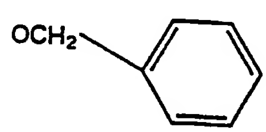
R_{50} is H or C_{1-3}alkyl;

R_{51} is H, C_{1-3}alkyl, halogen, OH, or OC_{1-3}alkyl; n is 1-3; and n' is 1 or 2; provided one of G and G' is H.

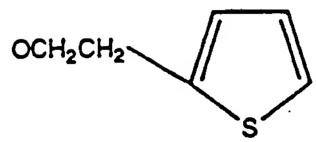
In preferred compounds:

B or B' is $OCH_2CH_2NHC(NH)NH_2$;

E is



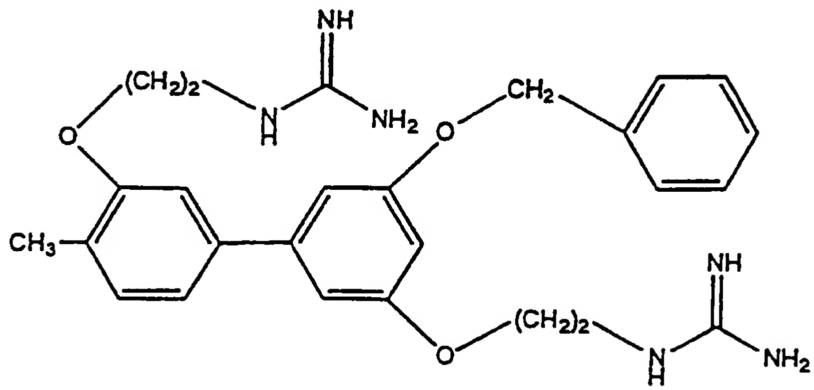
or



F or F'' are $OCH_2CH_2NHC(NH)NH_2$; and

G and G' are H.

Synthesis of the following preferred compound is included in the Examples below:



(1-methyl-2,5'-diethoxyguanidino-3'-oxybenzylbiphenyl)

These compounds are tested for bradykinin antagonist activity using a high-volume biochemical binding assay such as is referenced in the examples below. For potential use in rapid mass screening, a rat B2 receptor has been cloned by Jarnagin et al. (PNAS (1991) 88, 7724). It appears to be a 7-transmembrane domain G-protein coupled receptor with a molecular weight of 42 kD and 366 amino acids. Furthermore, a human B2 receptor was cloned by Hess et al. (Biochem. Biophys. Res. Comm. (1992) 184, 260) and has a molecular weight of 41.1 kD and 364 amino acids with 81% sequence homology to the rat B2 receptor. The binding assays are followed by examination of the compound in an in vitro smooth muscle preparation. Functional activity is assessed by examining in vitro PI turnover. In vivo models include bradykinin paw pressure in rats, both IP and PO.

Most of the remaining seven transmembrane G-protein coupled receptors (GPCR) are viable candidates for the approach described herein. Such receptors include, but are not limited to, CCK, angiotensin, bombesin, bradykinin, endothelin, neuropeptide Y, neurotensin, opiod, somatostatin, tachykinin (NK_1, NK_2, NK_3), thromboxane A_2, and

vasopressin. The angiotensin-2 receptor might be of particular interest as a test case in light of the recently reported activity of a number of functionalized bisphenyl molecules.

The ligands for many of the GPCRs range from small-medium sized organics to small-medium peptides (4-35 amino acids). Most of these ligands are expected to occupy a 10-30 cubic Å volume making them ideal candidates for the libraries described herein. An increasing number of modeling and mutagenesis studies are not only indicating the appropriate approximate size but are also giving specific information on important residues of the receptor that interact with the ligand. This information can be readily applied to the design of receptor specific subuniversal libraries.

Some examples of recently available information includes the TXA_2 receptor (Yamamoto et al., J. Med. Chem. (1993) 36, 820-25). These workers propose the TXA_2 binding site and suggest specific residues of the receptor that are important for ligand binding, including Ser-201, Arg-295, and Trp-258. Groups that are complimentary to these residues would be built into the sub-universal library.

The NK 1-3 receptors have been cloned and expressed and mutational studies are ongoing which suggest the binding site for NK_1 antagonists is likely to be around the junction of extracellular loop 2 and the top of TMV and TMVI. Furthermore, the identification of non-peptide leads for the NK-1 receptor suggests some groups that allow initial selection of groups for a sub-universal library (Watling, TIPS (1993) 14, 81). It is believed that NK_1 antagonists will be useful for treating pain, inflammation, arthritis, and asthma.

Identification of residues for design of a somatostatin sub-universal library is guided by the work of Hirschmann et al. (J. Amer. Chem. Soc. (1992) 114, 9217).

Preparation of compounds that interact with ion channels provides another example of designing a sub-universal library. Ion channels are proteins which span cell membranes providing pathways for the flow of ions such as chloride or potassium. These channel proteins are involved in many cellular functions such as nerve signaling, muscle contraction and hormone secretion. Over the past several years there has been an explosive growth in the number of cloned and expressed ion channels, as well as in discoveries which link channels to disease. Moreover, now that it is clear that there are many subtypes of ion channels differentially distributed throughout the body, the possibilities for selective targeting of specific channels in specific tissues are unlimited.

This selective targeting will reduce unwanted drug-related side effects and toxicities. The plasma membrane localization of ion channels eliminates the need for complex delivery systems required for drugs directed at intracellular or intranuclear targets.

Potassium channels can be divided into at least 6 major classes, and 15 subclasses, each with its own distinct biophysical and pharmacological identity. Agents which modulate specific potassium channels in specific tissues are expected to target select disease states without altering normal functions. Potassium channels are largely responsible for maintenance functions like establishing the membrane potential in unstimulated cells, or in switching on, or off, a cell's electrical activity. Thus, these channels in part control the cell's capacity for nervous transmission, muscle contraction and secretion. Due to their integral roles in almost all normal signal processing, agents which modulate potassium channels are likely to be useful for treating conditions such as diabetes and muscular sclerosis, cardiac arrhythmias and vascular hyperactivity.

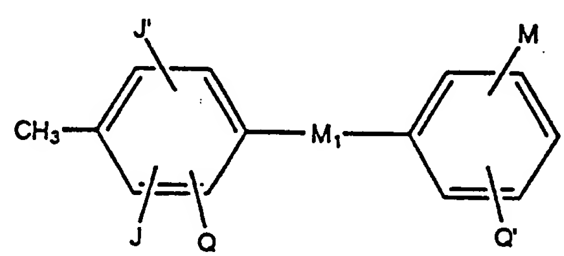
Various types of ligand-activated and voltage-activated ion channels have now been cloned and functionally expressed. Sequence comparisons and hydropathy analyses have revealed a great deal of structural homology among these channels. Each channel sequence is composed of a repeating motif of transmembrane spanning domains which combine in various ways to form channels (For a recent review of the field, see Andersen and Koeppe, II, Physiological Reviews (1992) Vol. 72).

Site-directed mutagenesis has allowed researchers to probe the primary structure of ion channel proteins for critical amino acid residues involved in the binding sites of drug molecules. These studies will allow for the development of agents targeted for specific channel subtypes and binding sites. To date, several classes of ion channels, including potassium and chloride, have received intensive characterization leading to a basis on which to consider structure-based drug design.

Toxins, such as those from scorpion venoms, have proven useful in defining potential drug interaction sites on ion channels as well as defining physiological roles for channels. These peptide toxins are 36-38 residues long, contain three disulfide bridges, and share strong sequence similarity among isoforms, block both voltage-gated and Ca-activated K channels with nanomolar affinity. Within this group of toxins, there are specific subtypes which bind to specific subtypes of potassium channels. Electrostatic interactions between charybdotoxin (CTX), a specific peptide pore blocker of K channels

and a Ca-activated K channel have been extensively investigated. Charybdotoxin has eight positively charged residues (four lysines, three arginines, and one histidine). Electrostatic forces are known to favor CTX binding to the negatively charged mouths of K channels. However, only replacement of Arg25, Lys27, or Lys34 with a Gln residue strongly decreased the affinity of the toxin for the channel. These three residues are located close to one another on one side of the CTX molecule and make direct contact with the channel mouth. On the opposite side are five charged residues whose neutralization show little effect. Therefore the positively charged groups on CTX promote toxin channel interaction in two ways; by weak through space electrostatic influences and by direct and intimate contact with the channel on one side of the toxin molecule. The solution structure of CTX has been recently determined (Bontems et al., Biochemistry (1992) 31, 7756) and it has been shown that Arg25 and Lys34 are located within 10Å of Lys27 and each is crucial for high affinity binding of CTX. The receptor site in the channel's mouth must be wide (>22Å) and flat to accommodate the CTX molecule. The wide mouth must narrow abruptly into an ion-selective pore in order to provide a selective K binding site with which Lys27 interacts (Miller and Park, Biochemistry (1992) 31, 749, and Neuron (1992) 9, 307). These studies reveal a molecular surface of CTX which makes direct contact with the extracellular mouth of the K channel and a single CTX molecule physically occludes the K conduction pathway by binding to a receptor located in the externally-facing mouth of the channel protein.

Using the information described above, a sub-universal library targeted to K channels which mimics the three important binding residues both electronically (three positive charges) and spatially (6-18Å total separation) is designed. Such a library is expected to identify non-peptide CTX mimics with therapeutic potential. The compounds of Formula IV represent a sub-universal library targeted to potassium channels.



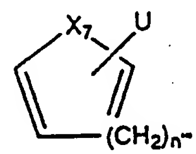
Formula IV

wherein:

M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

J, J', and M independently are $O(CH_2)_nNR_{50}C(NR_{51})NR_{52}R_{65}$ or $O(CH_2)_{n'}NR_{53}R_{54}$ wherein R_{50}, R_{51}, R_{52}, R_{53}, R_{54}, and R_{65} independently are H or C_{1-3}alkyl, and n and n' independently are 2-3;

Q and Q' are H or $O(C_{1-4}alkyl)T$ wherein T is C_{1-6}alkyl, CO_2R_{55}, OR_{56}, or



wherein:

X_7 is CH, N, NH, S, or O;

n''' is 1 or 2;

U is H, C_{1-6}alkyl, halogen, CF_3, or OR_{57}; and

R_{55}, R_{56}, and R_{57} independently are H or C_{1-6}alkyl; provided that Q or Q' is H.

The presently invented multiple combinatorial method for preparing and selecting small molecular weight compounds having pharmaceutical utility or other biologic utility is used to efficiently prepare universal libraries. As used herein a multiple combinatorial method is a method for preparing compounds that uses two or more scaffold molecules each carrying functional groups that have been attached in a combinatorial fashion. Generally, compounds comprising two scaffold moieties are used for ligates of about 12 to 20 Å and compounds having three scaffold moieties yield ligands for ligates of about 20 to 35 Å.

The power of the invented multiple combinatorial method is demonstrated by the numbers of compounds that can be prepared quickly and efficiently. For example, using two scaffold molecules each containing two of twenty possible functional groups arranged in four different orientations yields more than 1,000,000 compounds. Using the same parameters with a third scaffold molecule allows for preparation of a universal library containing more than 1,000,000,000 compounds. The compounds of Formula I are an example of a universal library of compounds that are prepared according to the invention.

In another aspect the invention is used to prepare large quantities of a desired target compound rather than small amounts of multiple compounds as is the case in

preparing universal or sub-universal libraries. Preferably when preparing universal or sub-universal libraries multiple compounds are prepared by simultaneously conducting different chemical reactions in multiple reaction vessels. Preferably, reactions are conducted simultaneously in about 25 reaction vessels, more preferably in about 100 reaction vessels, and most preferably in standard 96 well plates. To prepare large quantities of a selected compound the same reaction is carried out simultaneously in multiple reaction vessels. For example, 2',4,5'-trimethoxybiphenyl-4'-carboxylic acid, a compound known to exhibit estrogenic activity, (CA54:19584c (1959)) is prepared according to the invention as described in the Examples below.

The compounds and libraries of the invention preferably are prepared according to Scheme I below. In Scheme I the preferred method of synthesizing the compounds on a solid support is depicted. The libraries and compounds of the invention, however, also can be prepared using solution phase chemistry.

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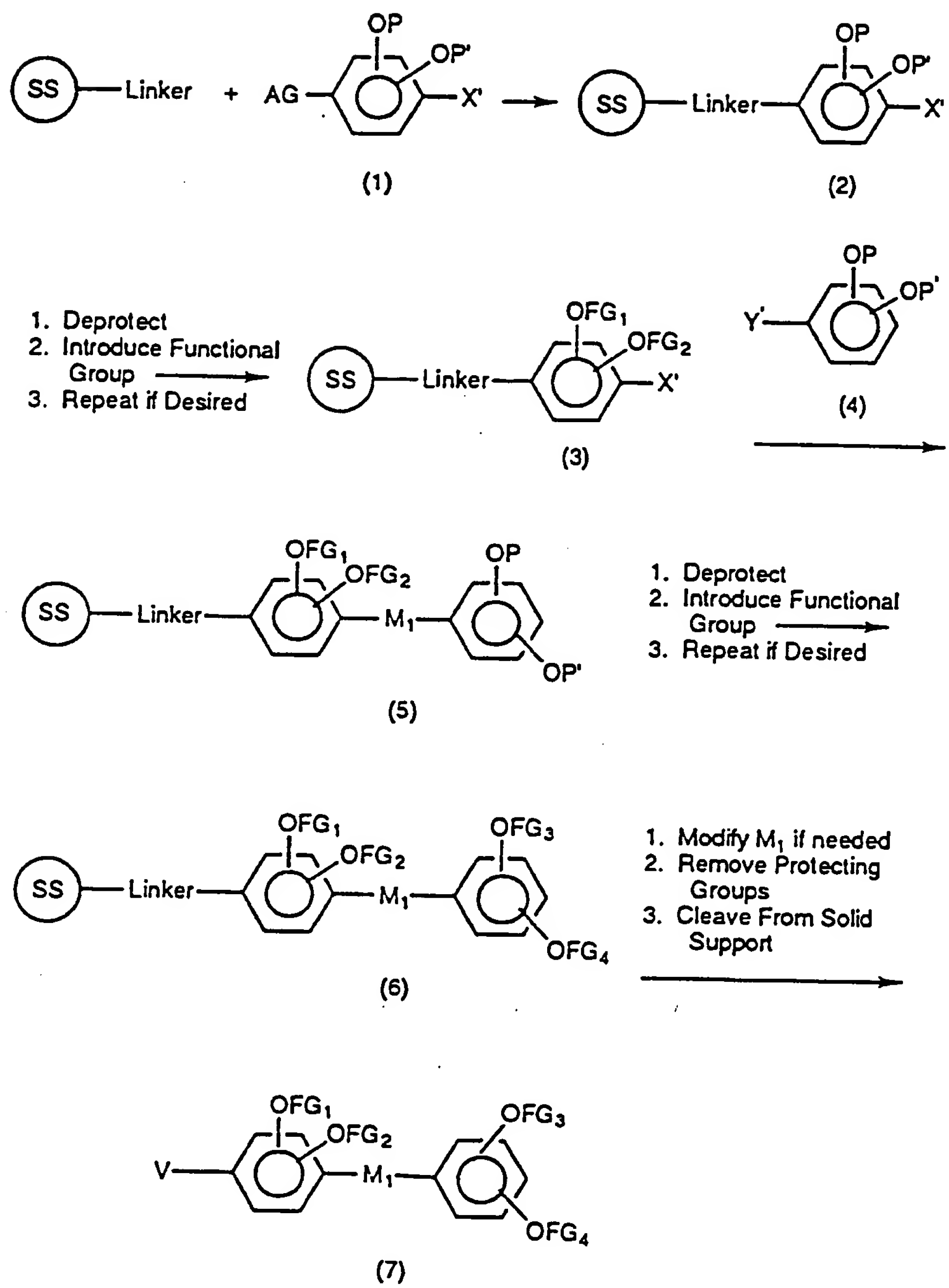
Scheme I


SS
Linker
AG
OP
OP'
X'
(1)
(2)
1. Deprotect
2. Introduce Functional Group
3. Repeat if Desired
OFG₁
OFG₂
Y'
(3)
(4)
M₁
(5)
OFG₃
OFG₄
(6)
1. Modify M₁ if needed
2. Remove Protecting Groups
3. Cleave From Solid Support
V
(7)

Scheme I demonstrates the invented method of preparing universal libraries of compounds. According to this scheme functional groups are attached to a first scaffold moiety to yield a compound comprising a scaffold and one or two functional groups (Compound 3). Thereafter a second scaffold molecule (Compound 4) is added followed by addition of functional group(s) to the second scaffold moiety to yield Compound 6 which can have 3 or 4 functional groups. Compounds of Formula I wherein M_1 is a bond then are prepared by cleaving Compound 6 from the solid support. Compounds of the invention wherein M_1 is CH_2, CH_2CH_2, CH=CH, or C≡C are prepared as described in Example 4.

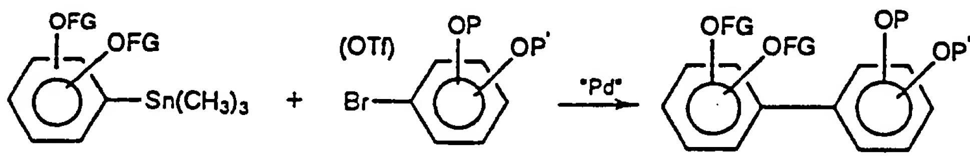
In Scheme I "SS" is a solid support material such as the crosslinked polystyrene resin known as the Merrifield resin (R. S. Merrifield, J. Am. Chem. Soc. (1963) 85, 2149). Alternatively, any other suitable polymeric resin or other support material such as, for example, silica, glass, cotton, and cellulose is used. Also in Scheme I "AG" is any suitable group for attachment to the linker such as, for example, OH, NH_2, COOH, CH_2Br, CHO, CH_2Cl, CH_2SH, SH, V and M_1 are the same as in Formula I.

The linker group shown in Scheme I is any group that can be reacted with the first scaffold (Compound 1) to attach it to a solid support, is stable to the reaction conditions necessary to complete the synthesis, and is easily cleavable upon completion of the synthesis. Suitable linkers are, for example, an OH, NH_2, halogen, SH, or COOH group. An olefin group also is used as a linker. In such case, for example, AG in Compound 1 is CHO and it is attached to the solid support using a Wittig-like reaction. When an olefin group is used the final product is cleaved from the linker by treatment with ozone or other known methods. A sulfide or oxygen bond is another suitable linker. When a sulfide or oxygen bond is the desired linker AG in Compound 1 is CH_2 halogen, preferably Br, and the bond between the solid support and Compound 1 is formed by reaction between the AG on Compound 1 and an SH or OH group on the solid support. Upon completion of the synthesis a sulfide or oxygen bond linker is cleaved by, for example, treatment with hydrogenolysis, Raney® nickel or dissolving metal reductions.

P and P' in Scheme I are protecting groups for aromatic hydroxy groups. P and P' can be the same or different to allow for selective deprotection. Choice of P and P' also is influenced by compatibility with the chemistry to be used in the remainder of the synthesis. Preferred protecting groups are $C(O)CH_3$ and Ph-CO wherein "Ph" is phenyl.

Deprotection of a $C(O)CH_3$ is performed by treatment with an amine according to known procedures and deprotection of a Ph-CO group is accomplished by treatment with a nucleophile such as methoxide using known conditions and procedures.

In Scheme I X' and Y' are groups that allow for attachment of the scaffold rings and introduction of the appropriate M_1 group. A preferred method for joining the rings is the method of Stille (J. Am. Chem. Soc. (1987) 109, 5478-5486) wherein X' and Y' are an organotin group and a halogen or triflate, respectively. The following is an example of using this method:



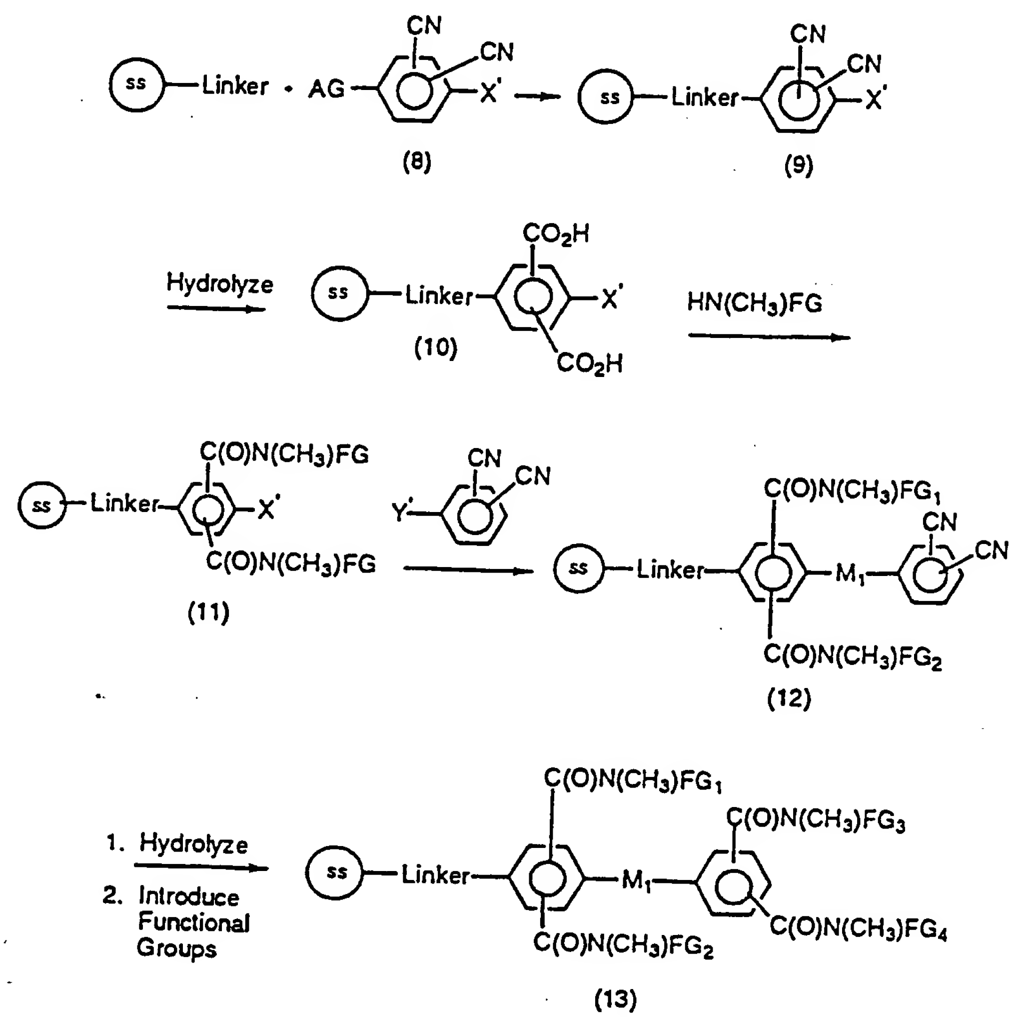
When compounds having more than two scaffold moieties are desired the procedure of Scheme I is modified by repeating the steps needed to add one or more additional scaffolds before cleaving from the solid support. Also, the general procedure shown in Scheme I is used when scaffolds other than phenyl rings are used. Thus, any of the compounds included in Formula I can be prepared using Scheme I modified as may be necessary to accommodate different scaffold moieties. Any such necessary modifications are apparent to those skilled in the organic chemical synthetic arts.

As used in Scheme I "FG" is a functional group which may be the same or different at different positions on the compounds. Suitable functional groups are the R_1 through R_6 groups as defined in Formula I above. Although Scheme I shows preparation of compounds having two scaffold moieties and four functional groups such compounds having three functional groups are prepared by using a scaffold having one functional group in place of Compound 1 or Compound 4. Also, Compounds 1 and 4 provide for attachment of functional groups through an oxygen. By suitable replacement of these compounds a sulfur atom, a nitrogen atom, or an N-alkylamide group can be used in place of one or more of the oxygens. Procedures for introducing functional groups onto the scaffolds are included in the examples below.

Scheme II is a modification of the Scheme I procedure that is used to prepare compounds wherein the functional group is attached to the scaffold moiety using a

$(CH_2)_{n'}C(O)NR'$ and n' is 0 and R' is H or C_{1-6}alkyl. In Scheme II AG, X', Y', and FG have the same meanings as in Scheme I.

Scheme II

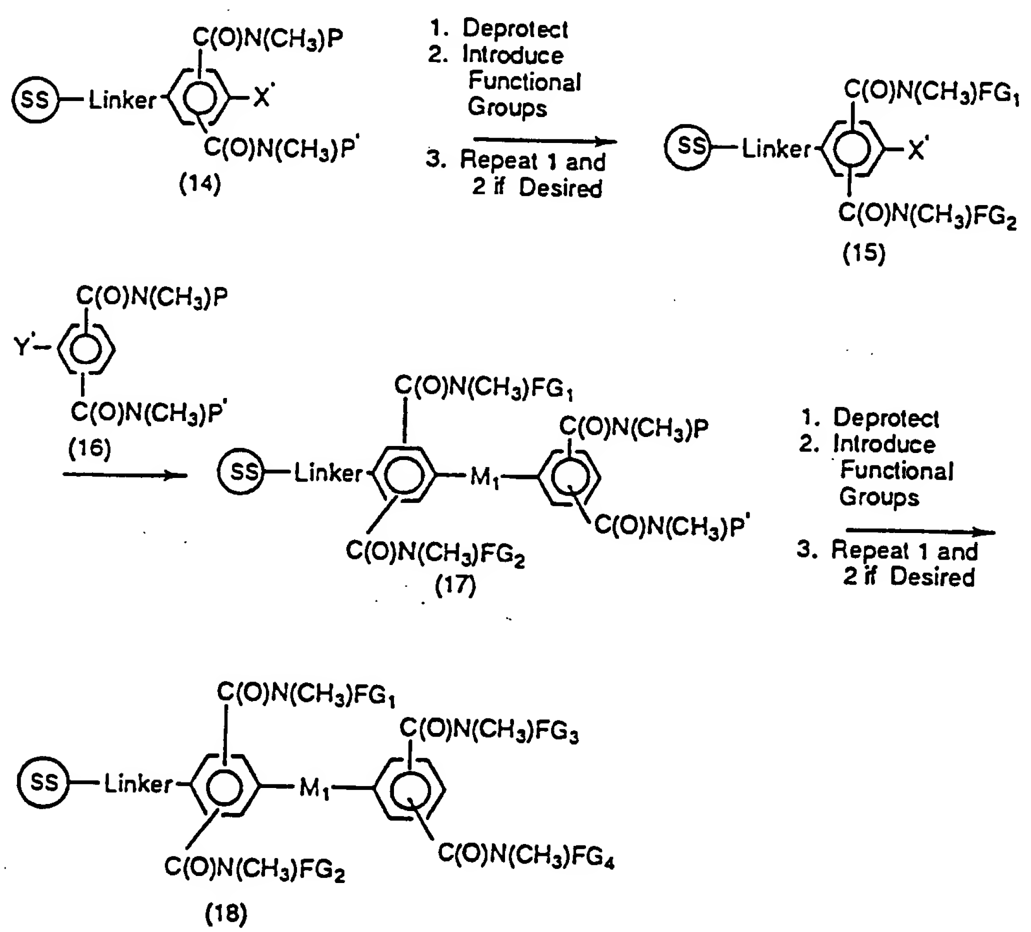


According to Scheme II a scaffold molecule having two cyano groups attached (Compound 8) first is attached to a solid support via a linker and then is hydrolyzed to yield free carboxylic acid groups (Compound 10). Then, functional groups are attached by treatment with $HN(CH_3)FG$ to yield a scaffold with two functional groups (Compound 11). Next a second scaffold moiety with two cyano groups is attached as described in Scheme I followed by addition of functional groups to yield Compound 13. Compounds to be included in the libraries of the invention then are prepared by adjusting the M_1 group

as needed, deprotecting and cleaving Compound 13 from the solid support as described in Scheme I.

Scheme III is a variation of Scheme II wherein the scaffold moiety substituents are protected prior to addition of the functional groups. In Scheme III X', Y', P, P', and FG have the same meanings as in Scheme I.

Scheme III

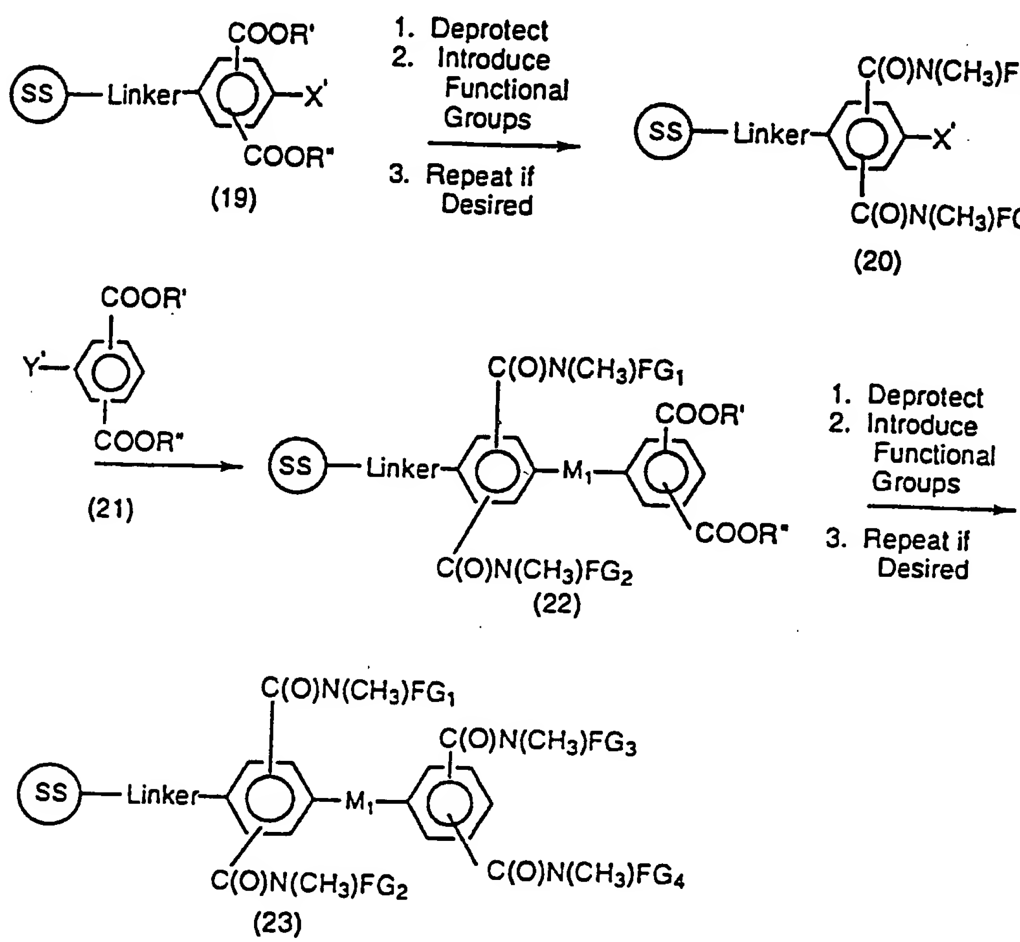


According to Scheme III Compound 14 is prepared by adding $HN(CH_3)P$ or $HN(CH_3)P'$ to the COOH functionalities of Compound 10 from Scheme II. Compound 15 then is prepared by deprotecting, differentially if desired, and introducing functional groups onto Compound 14. Compound 16 then is added to Compound 15 using the procedure for attaching scaffold moieties described in Scheme I to yield Compound 17.

Compound 18 next is prepared by deprotecting, differentially if desired, and introducing functional groups onto Compound 17. Compounds included in the invented libraries are prepared by adjusting the M_1 group as needed, deprotecting and cleaving Compound 18 from the solid support as described in Scheme I.

Scheme IV describes an alternate method of producing compounds wherein the functional groups are linked to the scaffold moieties via a $C(O)N(CH_3)$ residue. In Scheme IV X', Y', P, P', and FG have the same meanings as in Scheme I.

Scheme IV

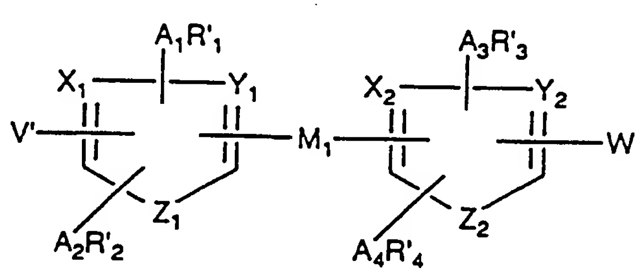


The starting compound in Scheme IV (Compound 19) is prepared by standard procedures. Compounds included in the invented libraries are prepared by cleaving Compound 23 from the solid support.

Alternatively, two or more scaffolds are independently derivatized with one or two functional groups, then are combined in a convergent approach. In a preferred method of this approach, two scaffolds are independently attached through a separate linker to a separate solid support material. The linkers and solid supports can be the same or different. The scaffolds can have handles for introducing side chains that are optionally protected or differentiated as described herein. After the attachment of one or two functional groups to each scaffold, one derivatized scaffold can be cleaved from its solid support, then reattached to the other scaffold through an appropriate coupling reaction. After any additional desired or needed synthetic transformations (e.g., side chain protecting group removal), the functionalized scaffold(s) is cleaved from the remaining solid support to give compounds of the invented libraries.

When compounds having more than two scaffolds are desired, a third scaffold can be independently functionalized, then coupled in the desired manner to one or both of the other scaffolds attached to a solid support or a combination of the two strategies can be employed whereby two scaffolds are attached together on a solid support in the manner described in the Schemes herein (a linear approach), then a third functionalized scaffold derived from a separate solid support is attached. In any case two or more scaffolds can be separately functionalized in a parallel, simultaneous fashion.

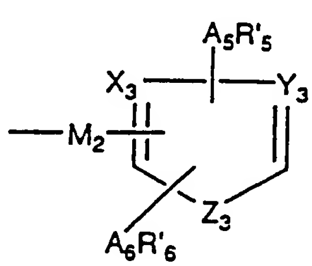
The disclosed invention includes the following Formula V compounds which are useful as intermediates in preparing the invented libraries and compounds:



Formula V

wherein:

W is H or



R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 are a protecting group or R_1, R_2, R_3, R_4, R_5, and R_6 as defined in Formula I, provided that at least one of R'_1 to R'_6 is a protecting group;

V' is V as defined in Formula I or a bond to a solid support; and

the remaining variables are as defined in Formula I.

As used in Formula V, a protecting group is any of the well known protecting groups that is suitable in view of the synthetic conditions used. Preferred protecting groups are $C(O)CH_3$ and Ph-CO.

Preparation of libraries of Formula I compounds is the first step in the invented method of preparing and selecting compounds having pharmaceutical or other biologic utility. After the libraries are prepared they are tested in a wide variety of in vitro and in vivo assays that are predictive of biologic activity and generally involve contacting the compounds with biological targets of interest and determining the strength of the interaction between the compounds and the biological target. Such assays are well known and include, without limitation, enzyme inhibition assays, such as protein kinase C and angiotensin converting enzyme, receptor binding assays, such as serotonin and excitatory amino acids, ion channel blocking, such as calcium, potassium and chloride, and transcription factor interaction. Generally, any activity identified in vitro is confirmed by evaluation in a suitable animal model if such is available and predictive of human pharmaceutical activity. The examples below include assays that are useful to select compounds of the invention that have pharmaceutical utility.

The compounds of Formula I that are useful as pharmaceutical agents can be incorporated into convenient dosage unit forms such as capsules, tablets, or injectable preparations. Pharmaceutical carriers which can be employed include, among others, syrup, peanut oil, olive oil, and water. Similarly, the carrier or diluent may include any time delay material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier will vary widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule, or an aqueous or non-aqueous suspension.

Pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary,

for tablet forms, or mixing, filling, and dissolving the ingredients, as appropriate, to give the desired oral or parenteral end products.

Doses of the pharmaceutically useful compounds of the invention will be an effective amount, that is, an amount necessary to produce the desired effect without producing untoward toxicity selected from the range of 0.1-1000 mg/kg of active compound, preferably 10-100 mg/kg. The selected dose is administered to a patient in need of treatment from 1-5 times per day, orally, rectally, by bolus injection, or by infusion.

EXAMPLES

The following examples illustrate but do not limit the scope of the invention disclosed in this specification.

EXAMPLE 1

General Procedures for Formula I Compounds Wherein M_1 is a Bond

Introduction of the phenyl ring onto the solid support: Merrifield resin (5g; containing 1.42 mmol Cl/g) and the appropriately substituted stannylated benzyl alcohol (for general procedures useful in the preparation of stannylated benzyl alcohols see: Wynberg and Meijer, Org. React. (1982) 65, 1; Hodgson et al., J. Amer. Chem. Soc. (1929) 1639, and Aziaian, J. Orgmetal. Chem. (1981) 215, 49) (25 mmol) in 60 mL of dry pyridine was stirred at room temperature for 48h. The polymer was filtered in air, washed with 4 x 25 mL pyridine, 25 mL ether, washed in a Soxhlet extractor for 8 h with ether and dried in vacuo.

Removal of the acetate group and introduction of the functional group-containing side chain: The resin bound material was placed in acetone and 2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al., J. Chem. Soc. (1964) 2137). The resin was filtered, washed and subjected to the following general alkylation scheme (Venuti et al., J. Med. Chem. (1988) 31, 2132). The resin-bound material (8.3 mmol) was placed in a mixture of 100mL $CHCl_3$, 50mL MeOH and anhydrous powdered potassium carbonate (5.0g, 36.18 mmol) was added (18-crown-6 can be added if solubility is a problem). The reaction was heated at

50°C for 15 min, then side chain bromide (9.24 mmol) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

Preparation of 3-benzyloxy-5-acetoxyphenol triflate: Phloroglucinol (16.2g, 0.1 mol) was dissolved/suspended in H_2O. The pH was adjusted to 8 with 10% NaOH. Bromobenzene (300 mL) was added and NaOH (60 mL) and benzoyl chloride (18 mL) were added via dropping funnel together over 30 min. The reaction was stirred for an additional 1 hr, filtered, washed with 150 mL bromobenzene and then twice with 500 mL warm water until the filtrate was pH 7. The water washings were back extracted with ethyl acetate (2 x 50 mL), dried and evaporated. The combined solids were dried in vacuo and recrystallized from 90mL ethyl acetate and 80 mL hexane to afford 7.7g (33% unoptimized) of desired product. This material (21.8g, 94.6 mmol) was dissolved in CH_2Cl_2 (220 mL) and triethylamine (66 mL, 0.473 mol) and acetic anhydride (26.78 mL, 0.283 mol) was added. The reaction was cooled in an ice bath and DMAP (2.31 g) added. The mixture was stirred overnight and allowed to warm to room temperature during this period. The reaction was diluted with ethyl acetate, washed with sat NH_4Cl, sat NaCl, back extracted with ethyl acetate, dried, and evaporated. The material remaining was purified by quick pass through silica gel; eluting with hexane/ethyl acetate 4:1. Obtained 29.59 g of desired product (99% yield). This material (1.0 g, 3.18 mmol) was dissolved in benzene (8 mL)/ethanol (10 mL) under argon. Potassium hydroxide (178 mg, 3.18 mmol) in ethanol (4 mL) was added dropwise over 10 min. The reaction was stirred for 10 min, diluted with ether and washed with 0.5M H_2SO_4, sat $NaHCO_3$, sat NaCl, back extracted with ether, dried and evaporated. The material was purified by flash chromatography (hexane/ethyl acetate 4:1). Obtained 0.91g, 82% yield of desired product. This material (5.86g, 21.5 mmol) was dissolved in CH_2Cl_2 and cooled in ice. Triethylamine (4.5 mL, 1.5 eq) followed by triflic anhydride (3.98 mL, 23.6 mmol) was added dropwise. To this final mixture was added DMAP (130 mg, 0.05 eq). After 5 min stirring the reaction was diluted with 500 mL ethyl acetate, washed with 0.5M H_2SO_4 (200 mL), sat $NaHCO_3$ (200 mL), sat NaCl, and back extracted with ethyl acetate. Dried, filtered, and evaporated. Purified via flash chromatography (W. C. Still et al., J. Org. Chem. (1978) 43, 2923) (hexane/ethyl acetate; 19:1) to afford 6.22 g, 72% yield of the desired triflate.

Palladium-Catalyzed Cross Couplings of Aryl Triflates with Organostannanes: General procedure (Saa et al., J. Org. Chem. (1992) 57, 678 and ibid (1993) 58, 1963).

The phenol triflate (0.5 mmol), anhydrous LiCl (0.171g, 4.2 mmol), triphenylphosphine (0.079g, 0.30 mmol), and $PdCl_2(PPh_3)$ (0.037g, 0.06 mmol) is suspended in DMF (4.5mL). The resin-bound organostannane was added and a crystal of inhibitor (2,6-di-tert-butyl-4-methylphenol) was added, and the mixture was then heated under an inert atmosphere of argon at 120°C for 2-8h. The resin was filtered and washed.

Removal of acetate group (a), introduction of side chain (b), removal of benzoate group (c), introduction of side chain (d):
Steps a, b, and d are carried out as described above. Removal of the benzoate is carried out as described by Bell (Tet. Lett. (1986) 27, 2263). The resin-bound material (0.005 mol) was placed in toluene (20 mL) and n-butylamine (3.65 g, 0.05 mol) was added. The mixture was stirred at room temperature for 3 h followed by filtration and washing of the resin.

Removal of all protecting groups: The resin-bound material was placed in CH_2Cl_2 (10 mL) and trifluoroacetic acid (0.5 mL) added. The mixture was stirred at room temperature for one hour then the resin filtered and washed.

Removal of the final product from the resin: Palladium (II) acetate (3 mol eq) was dissolved in warm (40°C) DMF (about 10 mL DMF/g of resin) and the resin added. After allowing 15 min for resin swelling and catalyst diffusion the reaction is shaken with hydrogen at atmospheric pressure. The resin turned black and hydrogen uptake continued for 24 h. The catalyst and resin were removed by filtration to afford the final product in DMF (Schlatter et al., Tet. Lett. (1977) 2851).

Preparation of Heteroaromatic Systems: The corresponding compounds where the phenyl ring is replaced with a heterocyclic ring can be synthesized by the same general procedures as described above with slight modification of the coupling step as described below. Each modification has strong precedent in the literature. As such, the systems containing all heterocyclic rings or a combination of phenyl and heterocyclic rings can be readily prepared. In general, the same type of chemistry that is used to couple two (or more) phenyl rings can be utilized to prepare the mixed, or pure, heterocyclic systems.

For example, Godard et al. (Tetrahedron (1992) 48, 4123) have demonstrated the phenyl-pyridyl and pyridyl-pyridyl coupling reactions in good to excellent yields using

either the Suzuki-type or Stille-type couplings utilized in the biphenyl construction, Furthermore, these authors carry out the reaction on O-alkyl substituted substrates in analogy with our proposed usage.

The following general procedure illustrates the coupling of a phenyl ring with a pyridine under Suzuki-type conditions: To the phenylboronic acid on resin (3.96 mmol of boronic acid) in toluene (20 mL) was added a solution of the iodopyridine (3.3 mmol), palladium tetrakis(triphenyl)phosphine (0.115 g, 0.1 mmol), sodium carbonate (3 mL aq 2M solution) in 1.7 mL ethyl alcohol and 20 mL toluene. The reaction was refluxed under argon for 12 h. The desired products were obtained after filtration and washing of the resin bound material.

The following procedure illustrates the coupling of pyridine rings with pyridine-like systems using the Stille procedure (taken from Godard et al.): To the (2-quinolyl)trimethylstannane (2.4 mmol based on the stannane) in dioxane (25 mL) was added a solution of 2-pyridyltriflate (2 mmol) and LiCl (0.254 g, 6 mmol) in dioxane (25 mL). Palladium tetrakis(triphenyl)phosphine (69 mg, 3%) was added and the mixture refluxed for 12-72 hr. Filtration and washing afforded the resin-bound product.

Terashima et al. (Heterocycles (1985) 23, 2375) have described the coupling of nitrogen-containing heterocycles with phenyl, pyridyl, thienyl, and furanyl compounds utilizing the reaction of a borane with a bromide under palladium catalysis. The reaction occurs when the groups are attached in the 2 and 3-positions of either ring system and therefore appears general in nature. The yields are moderate to good.

Finally, a review detailing the scope of coupling heterocyclic rings together can be found by Kalinin (Russ. Chem. Rev. (1991) 60, 339).

EXAMPLE 2

Preparation of 1-Methyl-2,5'-diethoxyguanidino-3'-oxybenzylbiphenyl

Preparation of intermediates:

4-(Trimethylstannyl)-2-acetoxybenzyl alcohol (A): Procedures used in the preparation of stannylated benzyl alcohols: Wynberg and Meijer, Org. React. (1982) 65, 1; Hodgson et al., J. Amer. Chem. Soc. (1929) 1639, and Aziaian, J. Orgmetal. Chem. (1981) 215, 49.

(2-N-PMC-guanidin)-(1-methanesulfonyl)ethanol (B): Ethanolamine (10.0g, 0.163 mol) was dissolved in CH_2Cl_2 (250 mL) and imidazole (24.41g, 0.358 mol) was added. The reaction was cooled to 0°C and TBDMS (27.14g, 0.18 mol) was added. The mixture was stirred at 0°C for two hours then room temperature for an additional two hours. Ethyl acetate (500mL) was added and the mixture washed with 0.5M H_2SO_4 (400mL), sat'd $NaHCO_3$ (400mL) and sat'd NaCl (400mL), dried, evaporated and the resulting material (12.0g, 42% yield) used as is. Formamidinesulfonic acid (1.0g, 8.05 mmol; Tet. Lett. (1988) 29, 3183) and the above material (1.41g, 8.05 mmol) were dissolved in dry methanol (10mL) and stirred for 2h at room temperature. The solvent was removed in vacuo and the product dissolved in acetone (27mL), water (7mL) and NaOH (10mL, 3.2M) added. The reaction was cooled to 0°C and PMCCl (3.66g, Raylo Chemicals, Alberta, Canada) was added in acetone (8mL). After stirring for 1h at 0°C the reaction was diluted with ethyl acetate, washed one time each with 25mL sat'd NH_4Cl, water, and sat'd NaCl, dried and evaporated. The product was purified by flash chromatography (silica, hexane/ethyl acetate 1:1) to afford 1.71g (46%) of desired product.

The product (0.57g, 1.23 mmol) was dissolved in THF (10mL), cooled to 0°C and tetrabutylammoniumfloride (371mg, 1.42 mmol) added. After 30 min the reaction was worked up by diluting with ethyl acetate, washing one time each with 25mL sat'd NH_4Cl, water, and sat'd NaCl, dried and evaporated. The product was purified by flash chromatography (silica, CH_2Cl_2/methanol; 19:1) to afford 0.43g (94%) of desired product. This material (64mg, 0.186 mmol) was dissolved in CH_2Cl_2 (2mL), cooled to 0°C and DMAP added (2.2mg). Methanesulfonyl chloride (35.6mg, 0.204 mmol) was added and reaction was complete after 20 min. Evaporation of the mixture was followed by purification (silica, CH_2Cl_2) to afford 95mg (92% yield) of desired product.

3-Benzyloxy-5-acetoxyphenol triflate (C): Phloroglucinol (16.2g, 0.1 mol) was dissolved/suspended in H_2O. The pH was adjusted to 8 with 10% NaOH. Bromobenzene (300 mL) was added and NaOH (60 mL) and benzoyl chloride (18 mL) were added via dropping funnel together over 30 min. The reaction was stirred for an additional 1 hr, filtered, washed with 150 mL bromobenzene and then twice with 500 mL warm water until the filtrate was pH 7. The water washings were back extracted with ethyl acetate (2 x 50 mL), dried and evaporated. The combined solids were dried in vacuo and

recrystallized from 90mL ethyl acetate and 80 mL hexane to afford 7.7g (33% unoptimized) of desired product. This material (21.8g, 94.6 mmol) was dissolved in CH_2Cl_2 (220 mL) and triethylamine (66 mL, 0.473 mol) and acetic anhydride (26.78 mL, 0.283 mol) was added. The reaction was cooled in an ice bath and DMAP (2.31 g) added. The mixture was stirred overnight and allowed to warm to room temperature during this period. The reaction was diluted with ethyl acetate, washed with sat NH_4Cl, sat NaCl, back extracted with ethyl acetate, dried, and evaporated. The material remaining was purified by quick pass through silica gel; eluting with hexane/ethyl acetate 4:1. Obtained 29.6 g of desired product (99% yield). This material (1.0 g, 3.18 mmol) was dissolved in benzene (8 mL)/ethanol (10 mL) under argon. Potassium hydroxide (178 mg, 3.18 mmol) in ethanol (4 mL) was added dropwise over 10 min. The reaction was stirred for 10 min, diluted with ether and washed with 0.5M H_2SO_4, sat $NaHCO_3$, sat NaCl, back extracted with ether, dried and evaporated. The material was purified by flash chromatography (hexane/ethyl acetate 4:1). Obtained 0.91g, 82% yield of desired product. This material (5.86g, 21.5 mmol) was dissolved in CH_2Cl_2 and cooled in ice. Triethylamine (4.5 mL, 1.5 eq) followed by triflic anhydride (3.98 mL, 23.6 mmol) was added dropwise. To this final mixture was added DMAP (130 mg, 0.05 eq). After 5 min stirring the reaction was diluted with 500 mL ethyl acetate, washed with 0.5M H_2SO_4 (200 mL), sat $NaHCO_3$ (200 mL), sat NaCl, and back extracted with ethyl acetate. Dried, filtered, and evaporated. Purified via flash chromatography (hexane/ethyl acetate; 19:1) to afford 6.22 g, 72% yield of the desired triflate.

N-t-Boc-1-bromoethylamine (D): Goel and Beylin, (Org. Prep. Proc. Int. (1987) 19, 78).

Preparation of Final Product:

Introduction of the phenyl ring (A) onto the solid support: Merrifield resin (5g; containing 1.42 mmol Cl/g) and stannylated benzyl alcohol (A, 25 mmol) in 60 mL of dry pyridine was stirred at room temperature for 48h. The polymer was filtered in air, washed with 4 x 25 mL pyridine, 25 mL ether, washed in a Soxhlet extractor for 8 h with ether and dried in vacuo.

Removal of the acetate group and introduction of the functional group-containing side chain (B): The resin bound material was placed in acetone and

2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al., J. Chem. Soc. (1964) 2137). The resin was filtered, washed. The resin-bound material (8.3 mmol) was placed in a mixture of 100mL $CHCl_3$, 50mL MeOH and anhydrous powdered potassium carbonate (5.0g, 36.18 mmol) was added (18-crown-6 can be added if solubility is a problem). The reaction was heated at 50°C for 15 min, then side chain mesylate (B, 9.24 mmol) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

Palladium-Catalyzed Cross Couplings of Aryl Triflate (C) with Resin-Bound A: The phenoltriflate (0.5 mmol), anhydrous LiCl (0.171g, 4.2 mmol), triphenylphosphine (0.079g, 0.30 mmol), and $PdCl_2(PPh_3)$ (0.037g, 0.06 mmol) is suspended in DMF (4.5mL). The resin-bound organostannane was added and a crystal of inhibitor (2,6-di-tert-butyl-4-methylphenol) was added, and the mixture was then heated under an inert atmosphere of argon at 120°C for 2-8h. The resin was filtered and washed.

Removal of acetate group (step a), introduction of side chain (B) (step b), removal of benzoate group (c), introduction of side chain (D)(step d):
Steps a, b, and d are carried out as described above with step d using side chain bromide (D). Removal of the benzoate is carried out as described by Bell (Tet. Lett. (1986) 27, 2263). The resin-bound material (0.005 mol) was placed in toluene (20 mL) and n-butylamine (3.65 g, 0.05 mol) was added. The mixture was stirred at room temperature for 3 h followed by filtration and washing of the resin.

Removal of all protecting groups: The resin-bound material was placed in CH_2Cl_2 (10 mL) and triflouroacetic acid (0.5 mL) added. The mixture was stirred at room temperature for one hour then resin filtered and washed.

Removal of the final product from the resin: Palladium (II) acetate (3 mol eq) was dissolved in warm (40°C) DMF (about 10 mL DMF/g of resin) and the resin added. After allowing 15 min for resin swelling and catalyst diffusion the reaction is shaken with hydrogen at atmospheric pressure. The resin turned black and hydrogen uptake continued for 24 h. The catalyst and resin were removed by filtration to afford the final product in DMF (Schlatter et al., Tet. Lett. (1977) 2851).

EXAMPLE 3

Preparation of 2',4,5'-Trimethoxybiphenyl-4'-carboxylic Acid

Preparation of intermediates:

4-(Trimethylstannyl)-2,5-diacetoxybenzoic acid (A): This compound is prepared from 4-bromo-2,5-diacetoxybenzoic acid whose preparation is described in Kamil et al., Pak. J. Sci. Ind. Res. (1971) 14, 59, by conversion of the bromo to the corresponding trimethylstannane following the general procedure of Aziaian (J. Orgmetal. Chem. (1981) 215, 49).

4-Methoxyphenol triflate (B): 4-Methoxyphenol (Aldrich, 1.24g, 10.0 mmol) was dissolved in CH_2Cl_2 and cooled in ice. Triethylamine (2.1 mL, 1.5 eq) followed by triflic anhydride (0.98 mL, 11.0 mmol) was added dropwise. To this final mixture was added DMAP (60 mg, 0.05 eq). After 5 min stirring the reaction was diluted with 50 mL ethyl acetate, washed with 0.5M H_2SO_4 (20 mL), sat $NaHCO_3$ (20 mL), sat NaCl, and back extracted with ethyl acetate. Dried, filtered, and evaporated. Purified via flash chromatography (hexane/ethyl acetate; 19:1) to afford 2.38 g (93%) yield of the desired triflate.

Preparation of the Final Product:

Introduction of the phenyl ring (A) onto the solid support: Merrifield resin (5g; containing 1.42 mmol Cl/g) and stannylated benzoic acid (A, 25 mmol) were reacted as described by Merrifield (J. Amer. Chem. Soc. (1963) 85, 2149). The polymer was filtered in air, washed with 4 x 25 mL pyridine, 25 mL ether, washed in a Soxhlet extractor for 8 h with ether and dried in vacuo.

Removal of the acetate group and introduction of the methyl groups: The resin bound material was placed in acetone and 2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al. J. Chem. Soc. (1964) 2137). The resin was filtered, washed. The resin-bound material (8.3 mmol) was exhaustively methylated with excess dimethylsulfate (5.23 g, 41.5 mmol; Org Synth. Coll. (1941) Vol. I, 58). After filtration, the residue was washed.

Palladium-Catalyzed Cross Couplings of Aryl Triflate (B) with Resin-Bound A: The phenoltriflate (0.5 mmol), anhydrous LiCl (0.171g, 4.2 mmol), triphenylphosphine (0.079g, 0.30 mmol), and $PdCl_2(PPh_3)$ (0.037g, 0.06 mmol) is

suspended in DMF (4.5mL). The resin-bound organostannane was added and a crystal of inhibitor (2,6-di-tert-butyl-4-methylphenol) was added, and the mixture was then heated under an inert atmosphere of argon at 120°C for 2-8h. The resin was filtered and washed.

Removal of the final product from the resin: The standard Merrifield procedure was employed (Merrifield, J. Amer. Chem. Soc. (1963) 85, 2149). The catalyst and resin were removed by filtration to afford the final product.

EXAMPLE 4

General Procedures for Preparation of Formula I Compounds Wherein M_1 is CH_2, CH_2CH_2, $CH=CH$, or $C\equiv C$

Schemes V and Va and the procedures which follow describe procedures for making the title compounds.

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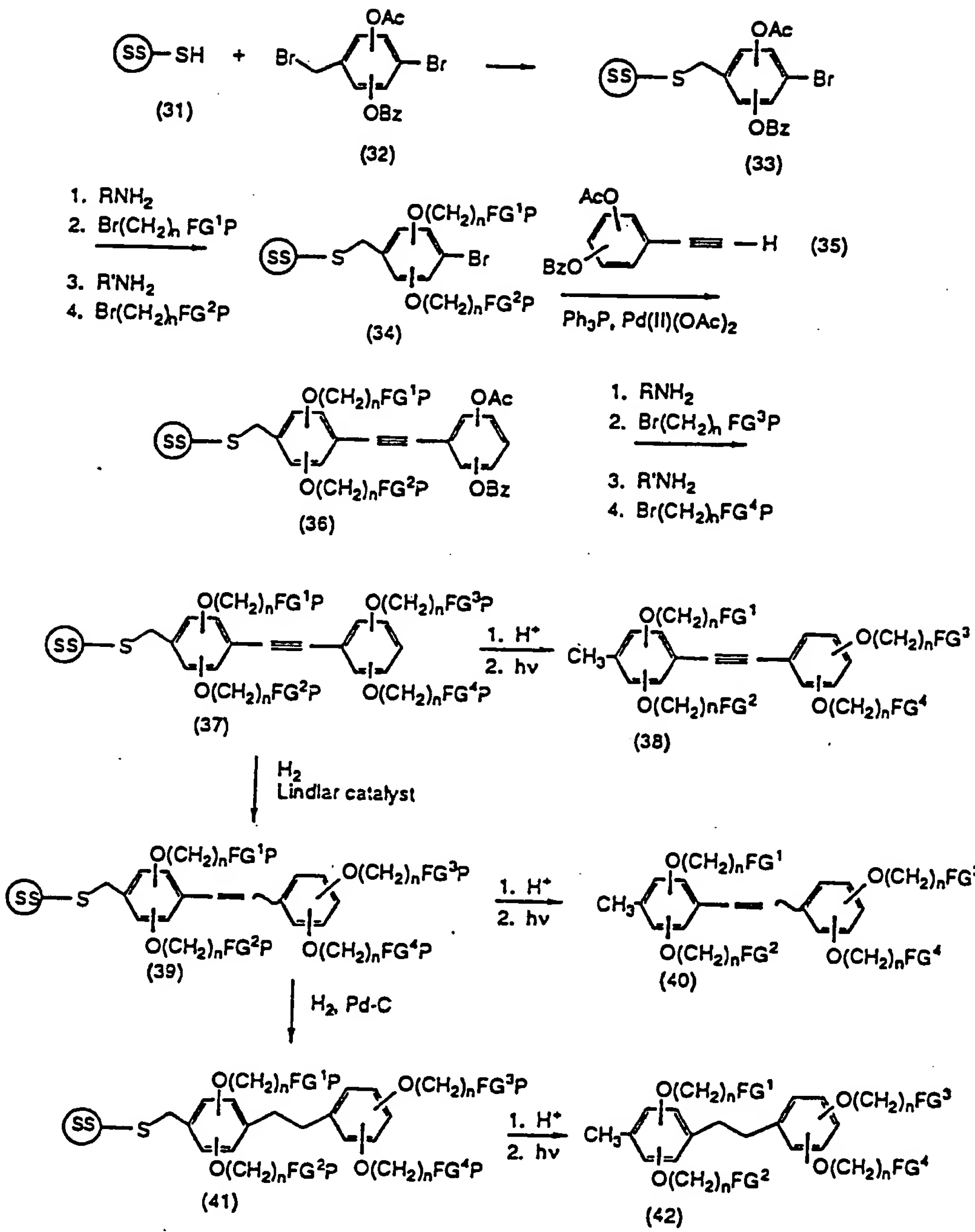
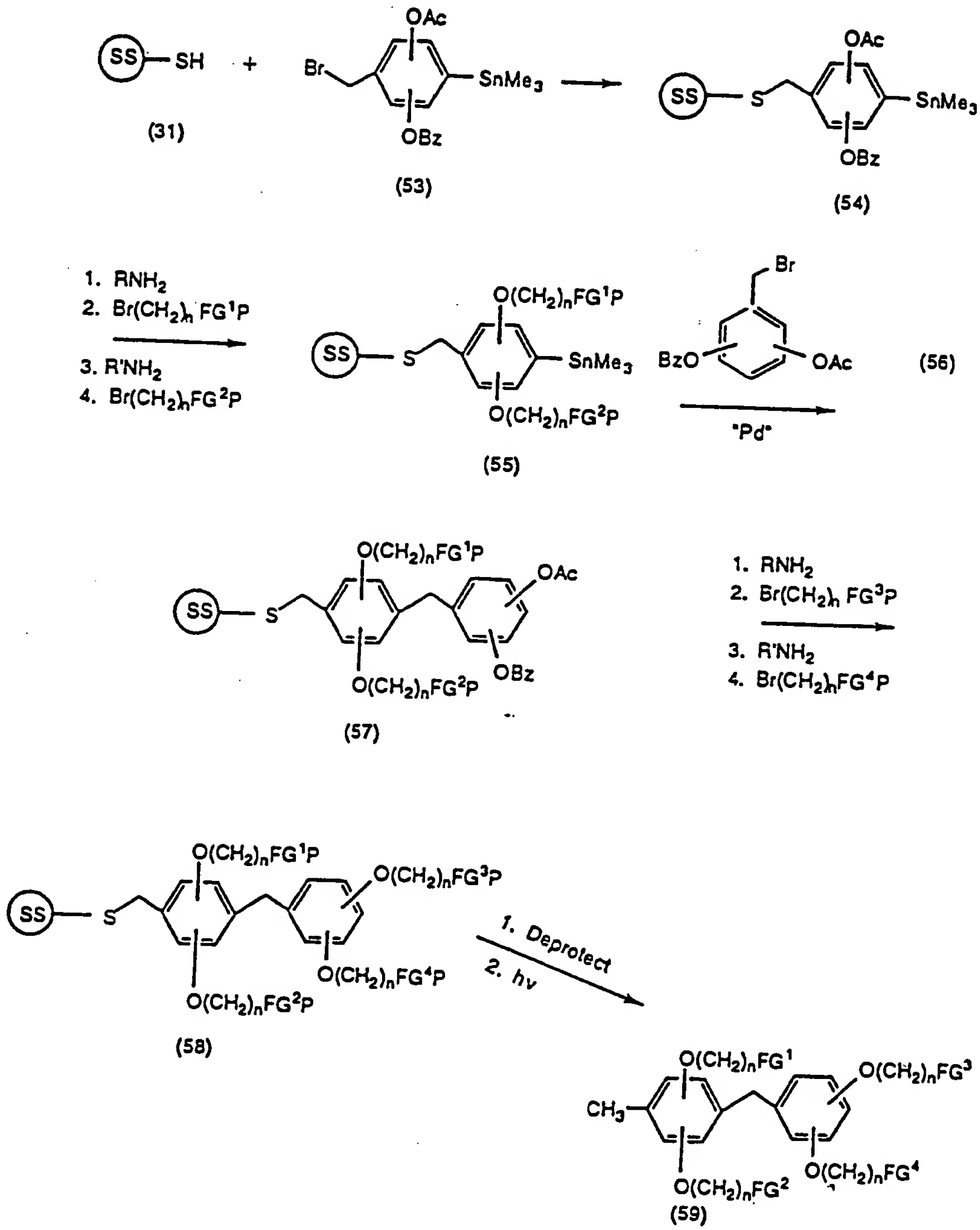
Scheme V


SS
SH
(31)
OAc
Br
Br
OBz
(32)
S
(33)
1. RNH2
2. Br(CH2)n FG1P
3. R'NH2
4. Br(CH2)nFG2P
O(CH2)nFG1P
O(CH2)nFG2P
(34)
AcO
BzO
H
(35)
Ph3P, Pd(II)(OAc)2
(36)
2. Br(CH2)n FG3P
4. Br(CH2)nFG4P
O(CH2)nFG3P
O(CH2)nFG4P
(37)
1. H+
2. hv
CH3
O(CH2)nFG1
O(CH2)nFG3
O(CH2)nFG2
O(CH2)nFG4
(38)
H2
Lindlar catalyst
(39)
(40)
H2, Pd-C
(41)
(42)

Scheme Va


SS
SH
(31)
Br
OAc
SnMe3
OBz
(53)
S
(54)
1. RNH2
2. Br(CH2)n FG1P
3. R'NH2
4. Br(CH2)nFG2P
O(CH2)nFG1P
O(CH2)nFG2P
(55)
Br
BzO
OAc
(56)
"Pd"
OAc
OBz
(57)
1. RNH2
2. Br(CH2)n FG3P
3. R'NH2
4. Br(CH2)nFG4P
O(CH2)nFG3P
O(CH2)nFG4P
(58)
1. Deprotect
2. hν
CH3
O(CH2)nFG1
O(CH2)nFG3
O(CH2)nFG2
O(CH2)nFG4
(59)

Preparation f resin, 31.

2-Methoxy methyl phenylacetate was prepared by refluxing 2-methoxy phenylacetate (10.2 g, 61.3 mmole), 70 mL of anhydrous methanol and 1.5 mL of concentrated sulfuric acid for 17 hours. The solvent was removed and the oil was dissolved in 100 mL of diethyl ether, washed with saturated $NaHCO_3$, dried, filtered and evaporated to give 9.26 grams (83%) of 2-methoxymethyl phenylacetate. This material (10.0 g, 55.0 mmole) dissolved in 6 mL of tetrachloroethane was added over a period of 25 minutes (making sure that the temperature of the reaction mixture did not exceed 50°C) to $AlCl_3$ (15 g, 112 mmole) in 50 mL of tetrachloroethane to which was added 2-bromopropionyl chloride (5.7 mL, 56.5 mmole) and the mixture heated at 45°C for 20 minutes. The reaction was allowed to stir at 50°C for 5 hours then at room temperature for 10 hours, poured onto 150 mL ice and 0.5 mL of concentrated HCl was added. The mixture was extracted with CH_2Cl_2 and the organic layer washed with 10% NaOH, and H_2O, dried, filtered and evaporated to give a dark purple-red oil which was purified by flash chromatography (SiO_2, first with 50% hexane-CH_2Cl_2 then with CH_2Cl_2) to afford 11.6 grams (66% yield) of methyl [3-(2-bromopropionyl)-6-methoxyphenyl]acetate as a thick oil: R_f= 0.44 (SiO_2, CH_2Cl_2). This material (11.4 g, 36.3 mmole) was dissolved in 70 mL of acetone and 15 mL of concentrated HCl, 20 mL of H_2O were added and the resulting solution refluxed for 6 hours. The volatiles were removed to give an oil/water mixture which was then dissolved in 100 mL of CH_2Cl_2. The mixture was extracted with 150 mL of saturated $NaHCO_3$. The aqueous was then removed and acidified with concentrated HCl to a pH = 1. The aqueous mixture was then quickly extracted with 100 mL of CH_2Cl_2. The organic layer was then dried, filtered, and evaporated to give 6.0 g (64%) of as a white solid: R_f = 0.6 (SiO_2, 10% methanol-CH_2Cl_2). To the sodium salt of 2-methyl-2-propanethiol (0.9 g, 8.82 mmole) was added sodium hydride (0.25g, 11.3 mmole) and 15 mL of anhydrous tetrahydrofuran and mixture cooled to 0°C. To the mixture was added the above 3-[(2-chloropropionyl)-6-methoxyphenyl]acetate (1.5g, 5.84 mmole) dissolved in 15 mL of anhydrous THF over a period of 10 minutes. After addition, the reaction mixture was stirred, at room temperature under nitrogen for 18 hours, the volatile components removed and dissolved in 80 mL of H_2O and the aqueous washed with 100 mL of diethyl ether. The aqueous layer was then acidified with 1 mL of concentrated HCl (pH=1) and extracted with ether. The organic layers were

combined, dried, filtered, and evaporated to give 1.75 grams of the t-butyl thioether product which was used without any further purification. To 1.75 g (5.64 mmole) of this material was added 2 mL of DMF, 4 mL of concentrated acetic acid, and 1 mL of H_2O. To the solution was then added 2-nitrobenzenesulfenyl chloride (1.6 g, 8.44 mmole) then stirred for 24 hours. The volatile components were removed under reduced pressure to give an oil/water mixture. To the mixture was then added 15 mL of H_2O, cooled to freezing, and then lyophilized overnight. After lyophilization, the remaining solid was taken up in CH_2Cl_2 and purified by flash chromatography (SiO_2, first with CH_2Cl_2, then with 50% diethyl ether-CH_2Cl_2 and then with 10% methanol-CH_2Cl_2) to isolate a yellow oil which crystallized upon standing to give 1.41 grams (59%) of a yellow crystalline solid: R_f = 0.37 (SiO_2, 10% methanol-CH_2Cl_2). Coupling of this material to TentaGel® resin was accomplished by placing TentaGel® (3.0g, 0.87 mmole of amine), 50 mL CH_2CL_2 and 1 mL DIEA (6.46 mmole) in a peptide synthesis vessel and the mixture shaken for 5 minutes followed by washing with CH_2Cl_2. To this was added 20 mL CH_2Cl_2 followed by 3-[2-[(2-nitrophenyl)dithio]propionyl]-6-methoxyphenylaceticacid from above (0.9 g, 2.2 mmole) dissolved in 30 mL of CH_2Cl_2 and mixture shaken for 30 seconds. To the mixture was added (0.3 mL, 2.1 mmole) diisopropylcabodiimide (DIC) and mixture shaken for 7 hours, filtered, washed with CH_2Cl_2, methanol, and CH_2Cl_2. The resin was then placed under pump vacuum for several hours to give 3.2 grams of the final resin material as a yellow solid. The amount of disulfide on the resin was determined by a modified Ellman spectrophotometric assay at 490 nm (0.18 mmole of disulfide/g of resin).

Introduction of the mono- or di-oxygen substituted bromobenzyl bromides 32, or mono- or di-oxygen substituted trialkylstannyl benzyl bromides 53, onto the resin to give 33 or 54: The mono- or di-oxygen substituted bromobenzyl bromides, 32 can be prepared by methods well known to those skilled in the art . For an example see Example 5 below. The trimethylstannyl group can be introduced if needed to afford 53, by reacting the penultimate intermediate to bromobenzene 32, the tolyl compound, (8.78 mmol) with $Pd(PPh_3)_4$ (71 mg, 0.061 mmol) in toluene (8.8 mL) to which was added hexamethylditin (5 g, 15.26 mmol). The reaction was heated to 120°C for 1.5h which after work-up and purification afforded the desired product. Conversion to the benzylbromide occurs with NBS under standard conditions.

To the above resin, 31 (2.3 g, 0.43 mmole) was added 150 mL DMF, β-mercaptoethanol (0.25 mL, 3.5 mmole) and diisopropylethylamine (0.4 mL, 2.3 mmole) and the mixture shaken for 2-3 minutes, filtered, and the process repeated two more times using the same quantities of BME and DIEA. The resin was then washed five times with DMF, three times with methanol, four times with CH_2Cl_2 and then three times with DMF. To the resin was then added 32 or 53 (1.21 mmole) dissolved in 15 mL DMF and DIEA (0.5 mL, 2.87 mmole) added and the mixture shaken for 6.5 hours, filtered, and washed five times with DMF, three times with methanol, and six times with CH_2Cl_2. The resin was then dried under pump vacuum to give 33 or 54.

Removal of acetate group, introduction of side chain, removal of benzoate group, and introduction of side chain to give 34 or 55: The resin bound material (46.0g, 8.3 mmol) was placed in acetone (300 mL) and excess 2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al., J. Chem. Soc., 2137 (1964)). The resin was filtered, washed, and subjected to the following general alkylation scheme (Venuti et al., J. Med. Chem. 31, 2132 (1988)):

The required bromides are either commercially available as needed, or as the bromide having side chains which require protection with standard acid labile protecting groups. Alternatively the alcohols are available which require conversion to the corresponding bromides or mesylates by methods known to those skilled in the art. In several cases the materials were prepared by a several step synthetic sequence as described in the specific example below.

The resin-bound material (46.0g, 8.3 mmol) was placed in a mixture of 300mL $CHCl_3$, 150mL MeOH and anhydrous powdered potassium carbonate (5.0g, 36.18 mmol) was added (18-crown-6 can be added if solubility is a problem). The reaction was heated at 50°C for 15 min, then side chain bromide (9.24 mmol) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

Removal of the benzoate is carried out as described by Bell (Tet. Lett., 27, 2263 (1986)). The resin-bound material (46.0g, 8.3 mmol) was placed in toluene (300 mL) and n-butylamine (3.65 g, 50 mmol) was added. The mixture was stirred at room temperature for 3 h followed by filtration and washing of the resin.

For introduction of the second functional group, the resin-bound material (46.0g, 8.3 mmol) was placed in a mixture of 300mL $CHCl_3$, 150mL MeOH and anhydrous

powdered potassium carbonate (5.0g, 36.18 mmol) was added (18-crown-6 can be added if solubility is a problem). The reaction was heated at 50°C for 15 min, then side chain bromide (9.24 mmol) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

EXAMPLE 4a

Preparation of Formula I Compounds Wherein M_1 is $C\equiv C$

Preparation of the substituted phenylacetylene 35 and conversion of 34 to 36: The substituted phenylacetylene 35 was prepared from the corresponding iodobenzene compound by the general procedure described by Lau et al. described below (J. Org. Chem., 1981, 46, 2280).

The differentially protected dihydroxyiodobenzene was prepared from the dimethoxyaniline (Aldrich) by diazotization and iodine introduction followed by demethylation of the methoxy groups all under standard conditions. Differential protection was accomplished from the iodophenol (16.0 mmol) which was dissolved in CH_2Cl_2 (30mL). Triethylamine (11.15mL, 80 mmol), acetic anhydride (4.55 mL, 48 mmol) and DMAP (390 mg, 3.2 mmol) were added and the reaction stirred for 16 h. The reaction was evaporated to dryness and this material (12.8 mmol) was dissolved in a mix of ethanol (32 mL) and benzene (16 mL). Potassium hydroxide (0.72g, 12.8 mmol) was dissolved in 8 mL ethanol and added over 30 min. After 30 min the reaction was diluted with ether, washed, dried, and evaporated. The monoacetate was dissolved in CH_2Cl_2 (50 mL) and triethylamine (3.45 mL, 24.8 mmol), DMAP (0.3g, 2.5 mmol) and benzoyl chloride (1.8 mL, 15.5 mmol) were added. The reaction was complete in 10 min then diluted with CH_2Cl_2, washed, and dried to afford the monoacetoxy monobenzoyloxyiodobenzene. This material (3 mmol) was placed together with TMS-acetylene (0.47g, 4.8 mmol), Pd(II)acetate (10 mg), and triphenylphosphine (20 mg) in dry triethylamine (5 mL). The mixture was heated at reflux for 4 h, cooled, the solid removed by filtration, the filtrate concentrated, mixed with sodium bicarbonate (20 mL), extracted with CH_2Cl_2, dried, and concentrated to afford the TMS-phenylacetylene. This material (2 mmol) was converted to the free acetylene by dissolving in THF (8 mL) and adding tetrabutyl ammonium fluoride (3 mL of 1M in THF) and stirring for 3h at room

temperature. After standard workup the desired substituted phenylacetylene 35 was obtained.

The resin bound bromobenzene 34 (16.5g, 3 mmol) was suspended in DMF (30 mL) and triethylamine (6 mL) added along with the acetylene 35 (8 mmol), Pd(II)acetate (20 mg), and triphenylphosphine (40 mg) in dry triethylamine (5 mL). The mixture was heated at reflux for 4 h, cooled, filtered, and washed in the standard fashion to afford 36.

EXAMPLE 4b

Preparation of Formula I Compounds Wherein M_1 is CH_2

Preparation of benzylbromide 56 and conversion of 55 to 57: The substituted benzylbromide 56 was prepared from the corresponding monoacetoxy-monobenzyloxytoluene by reaction with N-bromosuccinimide under standard conditions. The monoacetoxy-monobenzyloxy toluene was in turn prepared from the corresponding dihydroxytoluene by the same protection scheme used to prepare the phenylacetylene 35, above.

For the conversion of 55 to 57, the general procedure of Milstein and Stille (JACS (1979) 101, 4992) was employed. The resin-bound 55 (5.5g, 1 mmol; prepared as described above) was suspended in 10mL hexamethylphosphoramide. To this was added benzylchlorobis(triphenyl-phosphine)-palladium (II) (0.05 mmol) and the benzylbromide 56 (5 mmol). The reaction was heated to 65°C for 10h, cooled, filtered and washed in the usual fashion.

Completion of 38, 40, 42, 59.

Removal of acetate group, introduction of side chain, removal of benzoate group, and introduction of side chain to afford 37 or 58: The resin bound material (4.6g 0.83 mmol) was placed in acetone (20 mL) and excess 2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al., J. Chem. Soc., 2137 (1964)). The resin was filtered, washed, and subjected to the following general alkylation scheme (Venuti et al., J. Med. Chem. 31, 2132 (1988)):

The required bromides are either commercially available or as the bromide having side chains which require protection with standard acid labile protecting groups. Alternatively the alcohols are available which require conversion to the corresponding

bromides or mesylates by methods known to those skilled in the art. In several cases the bromides or mesylates were prepared via several step synthetic procedures such as that described in the specific example below.

The resin-bound material (4.6g, 0.83 mmol) was placed in a mixture of 20mL $CHCl_3$, 10mL MeOH and anhydrous powdered potassium carbonate (3.6 mmol) was added (18-crown-6 can be added if solubility is a problem). The reaction was heated at 50°C for 15 min, then side chain bromide (0.92 mmol) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

Removal of the benzoate is carried out as described by Bell (Tet. Lett., 27, 2263 (1986)). The resin-bound material (4.6g, 0.83 mmol) was placed in toluene (10mL) and n-butylamine (5.0 mmol) was added. The mixture was stirred at room temperature for 3 h followed by filtration and washing of the resin.

For introduction of the second functional group, the resin-bound material (4.6g, 0.83 mmol) was placed in a mixture of 20mL $CHCl_3$, 10mL MeOH and anhydrous powdered potassium carbonate (3.6 mmol) was added (18-crown-6 can be added if solubility is a problem). The reaction was heated at 50°C for 15 min, then side chain bromide (0.92 mmol) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

Reduction of the acetylene 37 to the olefin 39: This selective reduction of the acetylene to the corresponding olefin is accomplished with Lindlar catalyst prepared as described in Org. Syn. Coll., Vol. V, 880.

To the resin-bound 37 (5.5g, 1 mmol) in 10 mL hexane was added 10mg of Lindlar catalyst and 50mL of quinoline. The reaction vessel is evacuated and placed under a slight positive pressure of hydrogen gas for 3 hours. filtered, and washed to afford 39.

Reduction of the olefin 39 to the ethylene analogue 41: To the resin-bound 39 (5.5g, 1 mmol) in 10 mL ethyl acetate was placed 50mg of $Pd(OAc)_2$ and the reaction was subjected to a positive pressure of hydrogen gas for 6 h. The mixture was filtered and washed in the standard fashion to obtain 41.

Removal of all protecting groups from 37, 39, 41, and 58: The resin-bound material (11.0g, 2mmol) was placed in CH_2Cl_2 (100 mL) and triflouroacetic acid (0.5 mL)

added. The mixture was stirred at room temperature for one hour then the resin filtered and washed.

Removal of the final product from the resin to give 38, 40, 42, and 59: The resin (3.0 g, 0.6 mmol) suspended in 25 mL of acetonitrile. The stirred mixture was irradiated under nitrogen atmosphere using a Rayonet photochemical reactor (consisting of sixteen black light phosphor bulbs having a maximum wavelength intensity at 350 nm) for 4 hours. After irradiation, the mixture was filtered to afford the desired products 38, 40, 42 and 59 in solution.

EXAMPLE 5

Preparation of 1-[4-Methyl-3-ethoxyguanidinophenyl]-2-[3'-ethoxybenzyl-5'-ethoxyguanidinophenyl]ethane (70) and (4-Methyl-3-ethoxyguanidinophenyl)-(3'-ethoxybenzyl-5'-ethoxyguanidinophenyl)methane (87)

Scheme VI, Scheme VIa, and the procedures that follow describe preparation of the title compounds.

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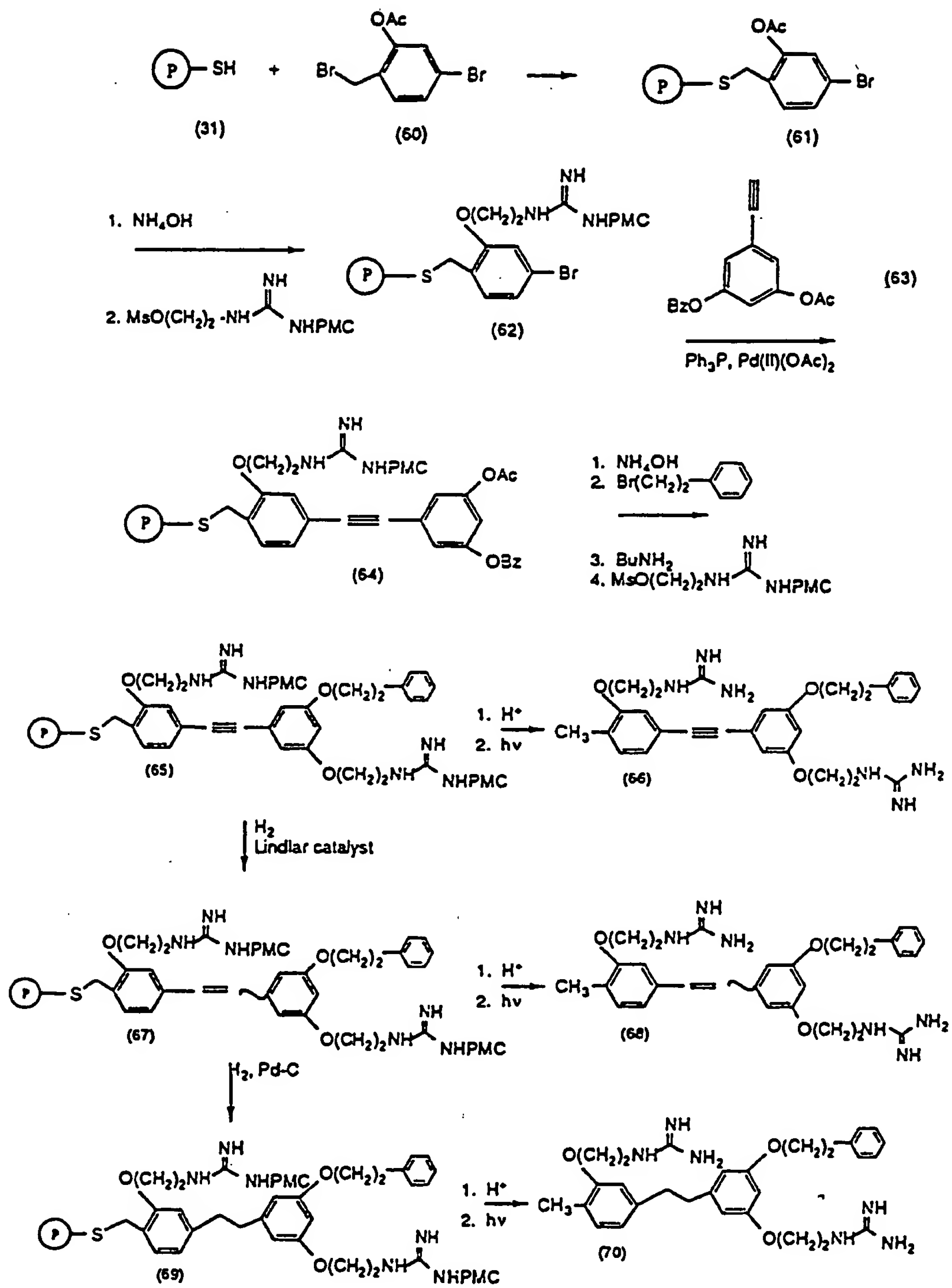
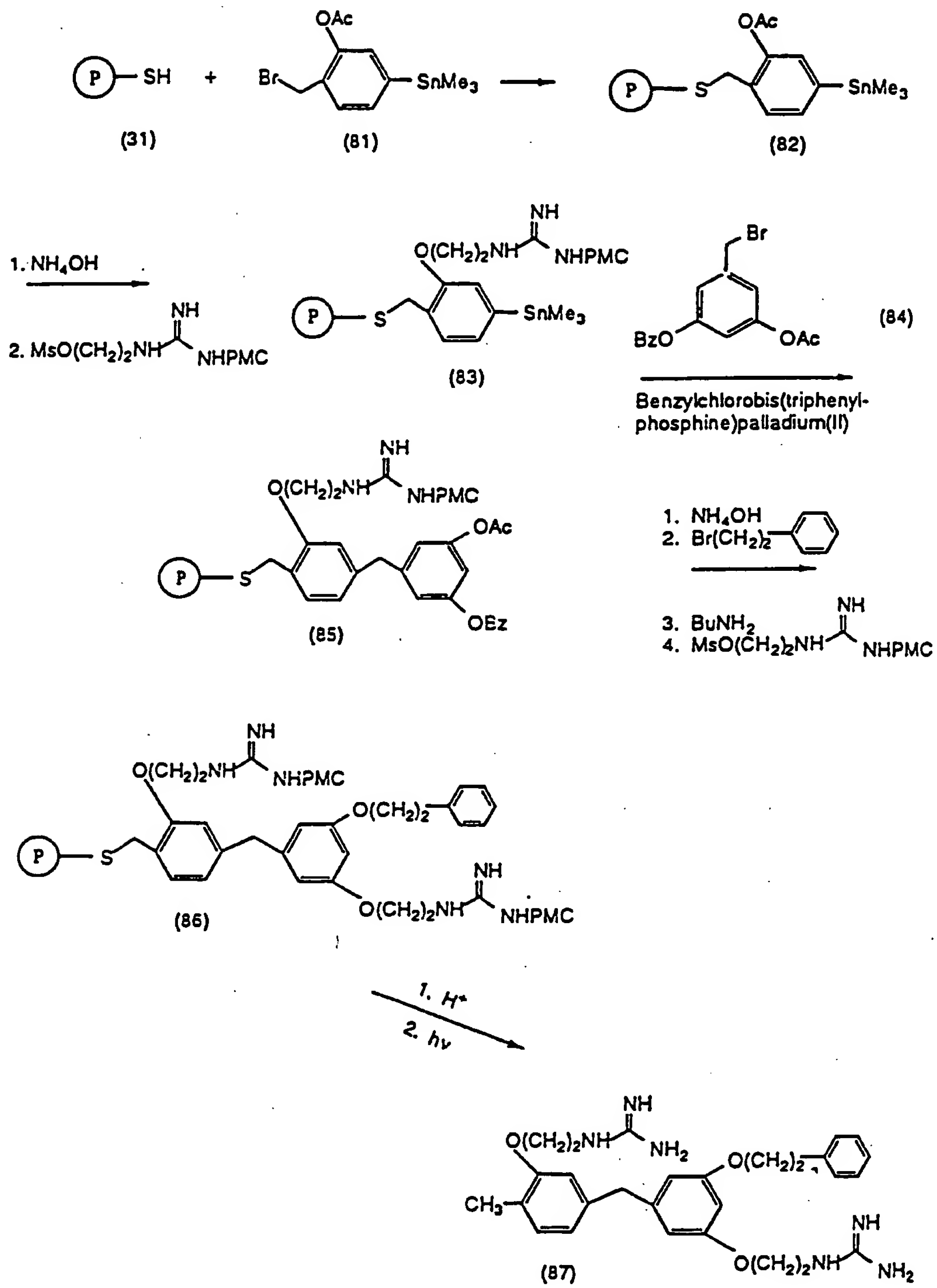
Scheme VI


(31)
(60)
(61)
1. NH_4OH
2. $MsO(CH_2)_2$-NH
NHPMC
(62)
(63)
Ph_3P, Pd(II)$(OAc)_2$
(64)
1. NH_4OH
2. $Br(CH_2)_2$
3. $BuNH_2$
4. $MsO(CH_2)_2NH$
(65)
1. H+
2. hv
(66)
H_2
Lindlar catalyst
(67)
(68)
H_2, Pd-C
(69)
(70)

Scheme VIa


OAc
SH
Br
SnMe3
(31)
(81)
(82)
1. NH4OH
2. MsO(CH2)2NH
NH
NHPMC
O(CH2)2NH
SnMe3
(83)
Br
BzO
OAc
(84)
Benzylchlorobis(triphenyl-phosphine)palladium(II)
OAc
OEz
(85)
1. NH4OH
2. Br(CH2)2
3. BuNH2
4. MsO(CH2)2NH
O(CH2)2
(86)
1. H+
2. hν
NH2
CH3
(87)

Intr ducti n f the 2-acetoxy-4-bromobenzylbromide, 60 or 2-acetoxy-4-trimethylstannylbenzylbromide, 81 onto resin 31 to give 61 or 82: Resin 31 is prepared as described in Example 3 above.

The starting materials 60 and 81 are prepared from commercially available materials by reactions well known to those skilled in the art of organic synthesis. For example, 2-acetoxy-4-bromobenzyl bromide is prepared from 2-methyl-5-nitroaniline (Aldrich) by diazotization under standard conditions. The diazo compound is thermolyzed in acetic acid for 1 h at 80°C as described in Chem. Lett., 1991, 459 to afford the corresponding acetoxy compound. The bromo group is introduced via nitro reduction, diazotization, and bromide displacement all under standard conditions and finally, the desired product is obtained by benzylic bromination with N-bromosuccinimide under standard conditions.

The corresponding trimethylstannyl derivative 81 is prepared from the penultimate intermediate above, 2-acetoxy-4-bromotoluene. The trimethyl stannyl group is introduced by placing the bromotoluene (2.0g, 8.78 mmol) in a dry flask with $Pd(PPh_3)_4$ (71 mg, 0.061 mmol). Toluene (8.8 mL) was added then hexamethylditin (5 g, 15.26 mmol) was added via syringe. The reaction was heated to 120°C for 1.5h. The reaction was cooled, filtered through Celite, and evaporated. The residue was dissolved in ether and washed with 3 x 50mL of 50% KF. The organic layers were dried (Na_2SO_4) and evaporated which after purification afforded the desired product (77% yield). Finally, the benzylic bromide is introduced by reaction with NBS under standard conditions.

The resin, 31 (2.3 g, 0.43 mmol) was suspended in 45 mL of anhydrous DMF. 15 mL DMF, b-mercaptoethanol (0.25 mL, 3.5 mmole) and diisopropylethylamine (0.4 mL, 2.3 mmole) were added and the mixture shaken for 2-3 minutes, filtered and the process repeated two more times using the same quantities of BME and DIEA. The resin was then washed five times with DMF, three times with methanol, four times with CH_2Cl_2 and then three times with DMF. To the resin was then added 60 (0.42g, 1.21 mmole) dissolved in 15 mL DMF and DIEA (0.5 mL, 2.87 mmole) added and the mixture shaken for 6.5 hours, filtered and washed five times with DMF, three times with methanol and six times with CH_2Cl_2. The resin was then dried under pump vacuum to give 2.2 grams of 61. The same procedure is used for the conversion of 81 to 82.

Removal of acetate group and introduction of side chain t give 62 and 83: The resin bound material 61 (4.6g. 0.83 mmol) was placed in acetone (30mL) and excess 2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al., J. Chem. Soc., 2137 (1964)). The resin was filtered, washed, and subjected to the following general alkylation scheme of Venuti et al. (J. Med. Chem. 1988, 31, 2132).

The resin-bound material (4.6g, 0.83 mmol) was placed in a mixture of 30mL $CHCl_3$, 15mL MeOH and anhydrous powdered potassium carbonate (0.5g, 3.62 mmol) was added. The reaction was heated at 50°C for 15 min, then (2-N-PMC-guanidino)-(1-methanesulfonyl)ethanol, (0.92 mmol, see preparation below) was added and the mixture refluxed for 4h. After filtration, the residue was washed in the standard fashion. To this material in THF (10 mL) was added tetrabutylammonium fluoride (2.0 mL of 1M solution in THF) and the reaction stirred at room temperature for 3h. After filtration and washing 62 was obtained. The same procedure was used for the conversion of 82 to 83.

Preparation of (2-N-PMC-guanidino)-(1-methanesulfonyl)ethanol: Ethanolamine (10.0g, 0.163 mol) was dissolved in CH_2Cl_2 (250 mL) and imidazole (24.41g, 0.358 mol) was added. The reaction was cooled to 0°C and TBDMSCl (27.14g, 0.18 mol) was added. The mixture was stirred at 0°C for two hours then room temperature for an additional two hours. Ethyl acetate (500mL) was added and the mixture washed with 0.5M H_2SO_4 (400mL), sat'd $NaHCO_3$ (400mL) and sat'd NaCl (400mL), dried, evaporated and the resulting material (12.0g, 42% yield) used as is. Formamidinesulfonic acid (1.0g, 8.05 mmol; Tet. Lett., 29, 3183, (1988)) and the above material (1.41g, 8.05 mmol) were dissolved in dry methanol (10mL) and stirred for 2h at room temperature. The solvent was removed in vacuo and the product dissolved in acetone (27mL), water (7mL), and NaOH (10mL, 3.2M) added. The reaction was cooled to 0°C and PMCCl (3.66g, Raylo Chemicals, Alberta, Canada) was added in acetone (8mL). After stirring for 1h at 0°C the reaction was diluted with ethyl acetate, washed one time each with 25mL sat'd NH_4Cl, water, and sat'd NaCl, dried and evaporated. The product was purified by flash chromatography (silica, hexane/ethyl acetate 1:1) to afford 1.71g (46%) of desired product.

The product (0.57g, 1.23 mmol) was dissolved in THF (10mL), cooled to 0°C and tetrabutylammoniumfluoride (371mg, 1.42 mmol) added. After 30 min the reaction was worked up by diluting with ethyl acetate, washing one time each with 25mL sat'd NH_4Cl, water, and sat'd NaCl, dried and evaporated. The product was purified by flash chromatography (silica, CH_2Cl_2/methanol; 19:1) to afford 0.43g (94%) of desired product. This material (64mg, 0.186 mmol) was dissolved in CH_2Cl_2 (2mL), cooled to 0°C and DMAP added (2.2mg). Methanesulfonyl chloride (35.6mg, 0.204 mmol) was added and reaction was complete after 20 min. Evaporation of the mixture was followed by purification (silica, CH_2Cl_2) to afford 95mg (92% yield) of desired product.

Preparation of disubstituted phenylacetylene 63 and formation of diphenyl acetylene 64: 3,5-Dihydroxyiodobenzene was prepared from 3,5-dimethoxyaniline (Aldrich) by diazotization and iodine introduction followed by demethylation of the methoxy groups all under standard conditions. This material (3.78g 16.0 mmol) was dissolved in CH_2Cl_2 (30mL). Triethylamine (11.15mL, 80 mmol), acetic anhydride (4.55 mL, 48 mmol) and DMAP (390 mg, 3.2 mmol) were added and the reaction stirred for 16 h. The reaction was evaporated to dryness, and passed through a plug of silica gel eluting with 4:1 hexane:ethyl acetate to afford the desired product. This material (12.8 mmol) was dissolved in a mix of ethanol (32 mL) and benzene (16 mL). Potassium hydroxide (0.72g, 12.8 mmol) was dissolved in 8 mL ethanol and added over 30 min. After 30 min the reaction was diluted with ether and washed with 0.5N H_2SO_4, sat $NaHCO_3$, sat NaCl, dried over Na_2SO_4 and evaporated. The product was recrystallized from toluene to afford 86% yield of the monoacetate which was dissolved in CH_2Cl_2 (50 mL) and triethylamine (3.45 mL, 24.8 mmol), DMAP (0.3g, 2.5 mmol) and benzoyl chloride (1.8 mL, 15.5 mmol) was added. The reaction was complete in 10 min then diluted with CH_2Cl_2 and washed with sat NH_4Cl, sat $NaHCO_3$, and sat NaCl. The solution was dried (Na_2SO_4) and evaporated. Purification was accomplished via silica chromatography 19:1 hexane:ethyl acetate to afford 4.4g (95% yield) of desired 3-acetoxy-5-benzoyloxy-iodobenzene.

The substituted phenylacetylene 63 was prepared from this iodobenzene by the general procedure described by Lau et al. (J. Org. Chem., 1981, 46, 2280).

The iodobenzene (1.15g, 3 mmol) was placed together with TMS-acetylene (0.47g, 4.8 mmol), Pd(II)acetate (10 mg), and triphenylphosphine (20 mg) in dry triethylamine

(5 mL). The mixture was heated at reflux for 4 h, cooled, the solid removed by filtration, the filtrate concentrated, mixed with sodium bicarbonate (20 mL), extracted with CH_2Cl_2, dried, and concentrated to afford the TMS-phenylacetylene. This material was converted to the free acetylene by dissolving in THF (8 mL) and adding tetrabutyl ammonium fluoride (3 mL of 1M in THF) and stirring for 3h at room temperature. After standard workup and chromatographic purification the desired substituted phenylacetylene 63 was obtained.

The resin bound bromobenzene 62 (5.5g, 1 mmol) was suspended in DMF (10 mL). To this suspension was added the acetylene 63 (0.85g, 3 mmol), Pd(II)acetate (10 mg), and triphenylphosphine (15 mg) in dry triethylamine (5 mL). The mixture was heated at reflux for 4 h, cooled, filtered, and washed in the standard fashion to afford 64.

Preparation of benzylbromide 84 and conversion of 83 to 85: The substituted benzylbromide 84 was prepared from the corresponding 3-acetoxy-5-benzyloxytoluene by reaction with N-bromosuccinimide under standard conditions. 3-Acetoxy-5-benzyloxytoluene was in turn prepared from orcinol (Aldrich) by the same protection scheme used to prepare the phenylacetylene 63, above.

For the conversion of 83 to 85, the general procedure of Milstein and Stille (JACS, 1979, 101, 4992) was employed. The resin-bound 83 (5.5g, 1 mmol; prepared as described above) was suspended in 10mL hexamethyl-phosphoramide. To this was added benzylchlorobis(triphenylphosphine)-palladium(2) (0.05 mmol) and the benzylbromide 84 (1.75g, 5 mmol). The reaction was heated to 65°C for 10h, cooled, filtered and washed in the usual fashion to afford 85.

The following conditions apply to 64 and 85 to afford 65 and 86.

Removal of acetate group, introduction of side chain, removal of benzoate group, and introduction of side chain to afford 65 and 86: The resin bound material (4.6g, 0.83 mmol) was placed in acetone (30 mL) and excess 2N ammonium hydroxide was added and the solution left at room temperature for 24 h (Haslam et al., J. Chem. Soc., 2137 (1964)). The resin was filtered, washed and subjected to the following general alkylation scheme (Venuti et al., J. Med. Chem. 31, 2132 (1988)):

The resin-bound material (4.6g, 0.83 mmol) was placed in a mixture of 30mL $CHCl_3$, 15mL MeOH and anhydrous powdered potassium carbonate (0.5g, 3.6 mmol) was added. The reaction was heated at 50°C for 15 min, then (2-bromoethyl)benzene (171mg,

0.92 mmol, Aldrich) was added and the mixture refluxed for 4h. After filtration, the residue was washed.

Removal of the benzoate is carried out as described by Bell (Tet. Lett., 27, 2263 (1986)). The resin-bound material (4.6g, 0.83 mmol) was placed in toluene (30 mL) and n-butylamine (0.37 g, 5.0 mmol) was added. The mixture was stirred at room temperature for 3 h followed by filtration and washing of the resin.

For introduction of the second functional group, the resin-bound material (4.6g, 0.83 mmol) was placed in a mixture of 30mL $CHCl_3$, 15mL MeOH and anhydrous powdered potassium carbonate (0.5g, 3.6 mmol) was added. The reaction was heated at 50°C for 15 min, then (2-N-PMC-guanidino)-(1-methanesulfonyl)ethanol, (0.92 mmol, see preparation above) was added and the mixture refluxed for 4h. After filtration, the residue was washed in the standard fashion.

Reduction of the acetylene 65 to the olefin 67: This selective reduction of the acetylene to the corresponding olefin is accomplished with Lindlar catalyst prepared as described in Org. Syn. Coll., Vol. V, 880. To the resin-bound 65 (5.5g, 1 mmol) suspended in 10 mL hexane was added 10mg of Lindlar catalyst and 50mL of quinoline. The reaction vessel is evacuated and placed under a slight positive pressure of hydrogen gas for 3 h, filtered, and washed to afford 67 (expected to be exclusively the Z-olefin).

Reduction of the olefin 67 to the ethylene analogue 69: To the resin-bound 67 (5.5g, 1 mmol) suspended in 10 mL ethyl acetate was added 50mg of $Pd(OAc)_2$ and the reaction was subjected to a positive pressure of hydrogen gas for 1 h. The mixture was filtered and washed in the standard fashion to obtain 69.

Removal of all protecting groups: The resin-bound material (11.1g, 2mmol) was placed in CH_2Cl_2 (100 mL) and trifluoroacetic acid (2.0 mL) added. The mixture was stirred at room temperature for one hour then the resin filtered and washed.

Removal of the final product from the resin to give 66, 68, 70, and 87: The resin bound material (3.3 g, 0.6 mmol) was suspended in 50 mL of acetonitrile. The stirred mixture was irradiated under nitrogen atmosphere using a Rayonet photochemical reactor (consisting of sixteen black light phosphor bulbs having a maximum wavelength intensity at 350 nm) for 4 hours. After irradiation, the mixture was filtered to afford the desired products 66, 68, 70, and 87 in solution.

EXAMPLE 6

Protein Kinase C Activity Determination

Compounds of the invention are tested for ability to inhibit protein kinase C using rat brain as the enzyme source accordingly to widely used procedures such as described by A. C. McArdle and P. M. Conn, Methods in Enzymology (1989) 168, 287-301, and by U. Kikkawa et al., Biochem. Biophys. Res. Commun. (1986), 135, 636-634. Alternatively, protein kinase C activity is determined using purified human protein kinase C isozymes by methods such as described in P. Basta et al., Biochim. Biophys. Acta. (1992) 1132, 154-160.

EXAMPLE 7

Membrane Receptor Affinity Determinations

A. Bradykinin Receptor

The bradykinin receptor affinity of compounds prepared according to this invention is determined by testing for ability to displace [^{3}H] bradykinin binding from guinea pig ileal membrane as described in S. G. Farmer et al., J. Pharmacol. Exp. Ther. (1989) 248, 677.

B. Other Receptors

Generally applicable methods for testing receptor affinity of the compounds of the invention are described by H. I. Yamamura et al., Methods in Neurotransmitter Receptor Analysis, Raven Press, 1990.

EXAMPLE 8

Measurement of Interaction with Target Enzymes

A. Angiotensin Converting Enzyme

Methods useful for determining the ability of compounds of the invention to inhibit angiotensin converting enzyme are disclosed by J. W. Ryan, Methods in Enzymology (1988) 164, 194-211.

B. Phospholipase A_2

A procedure useful to test efficacy of the invented compounds in inhibiting phospholipase A_2 is described by J. Reynolds et al., Methods in Enzymology (1991) 197, 3-23.

EXAMPLE 9

Determination of Ion Channel Binding

Xenopus oocytes are well known as tools for studying ion channels and receptors. A. L. Buller and M. M. White have described methods useful to measure interaction between compounds of the invention and various ion channels or receptors. Methods in Enzymology (1992) 207, 368-375.

EXAMPLE 10

Transcription Factor Effects

J. M. Gottesfeld is an example of a reference describing a procedure suitable for analyzing the ability of the invented compounds to influence transcription factor function. Methods in Enzymology (1977) 170, 346-359.

The disclosures of all references cited in this specification herein are incorporated in their entireties by reference.

What is claimed is:

1. A method for preparing and selecting non-peptide low molecular weight compounds having a desired biological utility that comprises:

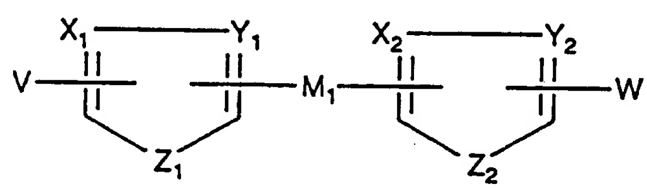
preparing a universal library of compounds having a molecular weight of about 200 to about 1000 daltons,

contacting compounds from the universal library with biological targets of interest, and

determining the strength of the interaction between the compounds and biological target.

2. A method of Claim 1 wherein the compounds have a molecular weight of between about 300 and about 600 daltons.

3. A method of Claim 2 wherein the compounds in the universal library each include a scaffold of the formula:



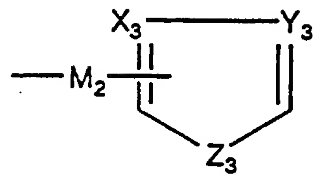
wherein:

M_1 and M_2 independently are a bond or CRR', CRR'CRR', CR=CR', or C≡C wherein R and R' independently are H or C_{1-6}alkyl;

X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

W is H or



X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH; and

V is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, or (C_{0-4}alkyl)NRR, or (C_{0-4}alkyl)CO_2R wherein each R independently is H or C_{1-6}alkyl.

4. A method of Claim 2 wherein the universal library is prepared by a method that comprises:

attaching at least one functional group to a first scaffold molecule,
attaching the second scaffold molecule to the first scaffold molecule, and
attaching at least one functional group to a second scaffold molecule.

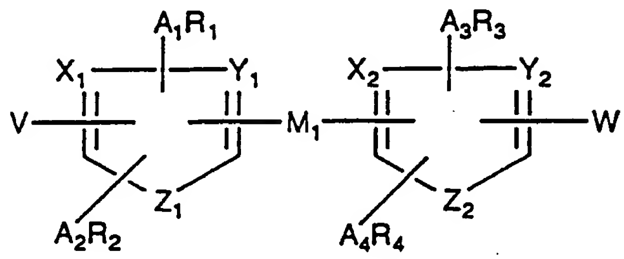
5. A method of Claim 4 that further comprises:
attaching a third scaffold molecule to the first or second scaffold molecule, and
attaching at least one functional group to the third scaffold molecule.

6. A method of Claim 4 wherein the first scaffold molecule is a phenyl ring.

7. A method of Claim 4 wherein the second scaffold molecule is a phenyl ring.

8. A method of Claim 5 wherein the first, second, and third scaffold molecules are phenyl rings.

9. A method of Claim 1 wherein the compounds in the universal library have the formula:

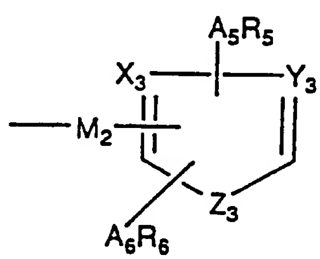


wherein:

X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

W is H or



X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

M_1 and M_2 independently are a bond or $CR_{84}R_{85}$, $CR_{84}R_{85}CR_{84}R_{85}$, $CR_{84}=CR_{85}$, or $C\equiv C$;

V is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, (C_{0-4}alkyl)$NR_{22}R_{23}$, or (C_{0-4}alkyl)CO_2R_{76};

A_1, A_2, A_3, A_4, A_5, and A_6 independently are absent or present as O, S, NR_{60}; or C_{0-6}alkylC(O)NR_{21}, provided that at least three are present;

R_1, R_2, R_3, R_4, R_5 and R_6 independently are H, C_{0-6}lkylCOR$_{15}$, C_{1-6}alkylR$_{16}$R$_{17}$, C_{1-6}alkylOR$_{24}$ except methoxymethyl, C_{1-6}alkylNR$_{25}$R$_{26}$, C_{0-6}alkylNR$_{80}$C(NR$_{81}$)NR$_{82}$R$_{83}$, C_{1-6}alkylindole, or C_{0-6}alkyl-D;

D is any one or multiple fused saturated or unsaturated five or six membered cyclic hydrocarbon or heterocyclic ring system containing one or more O, N, or S atoms that are unsubstituted or substituted by any accessible combination of 1 to 4 substituents selected from C_{1-6}alkyl, NR_7R_8, OR_9, SR_{10}, or COR_{11}, halogen, CF_3;

R_7, R_8, R_9, R_{10}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{60}, R_{80}, R_{81}, R_{82}, R_{83}, R_{84} and R_{85} independently are H or C_{1-6}alkyl;

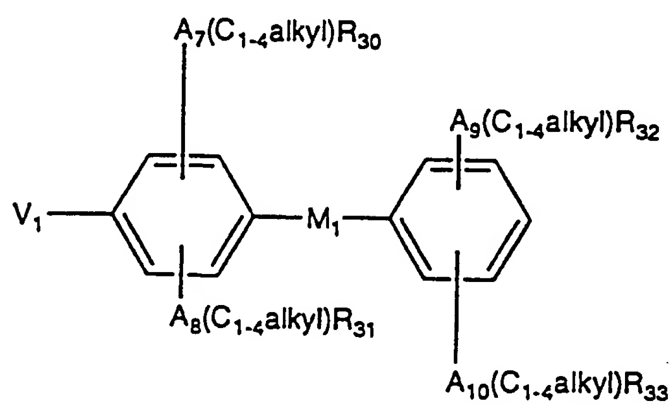
R_{12}, R_{13}, R_{14}, R_{16}, R_{17}, R_{18}, R_{24}, R_{25}, R_{26}, and R_{76} independently are H, C_{1-6}alkyl, phenyl, or substituted phenyl;

R_{11} is OR_{12} or $NR_{13}R_{14}$;

R_{15} is OR_{18} or $NR_{19}R_{20}$; or

any pharmaceutically useful salt thereof.

10. A method of Claim 9 wherein the compounds in the library have the formula:



wherein:

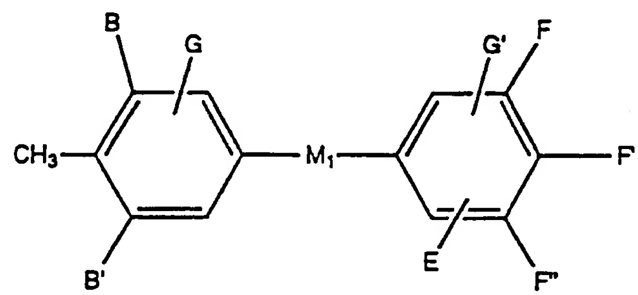
M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

V_1 is H, CH_3, OH or CH_2OH;

A_7, A_8, A_9, and A_{10} independently are absent or present as O provided that three are O; and

R_{30}, R_{31}, R_{32}, and R_{33} independently are OH, NH_2, CO_2H, phenyl, substituted phenyl, $CONH_2$, $NR_{80}C(NR_{81})NR_{82}R_{83}$, C_{1-6}alkyl, imidazole, or indole wherein R_{80} to R_{83} are H or C_{1-4}alkyl.

11. A method of Claim 9 wherein the compounds in the library have the following formula:

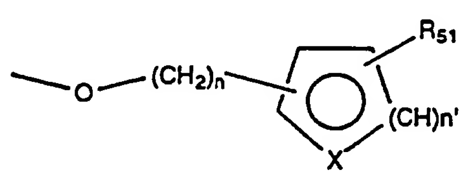


wherein:

M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

B and B' are H, $O(CH_2)_nNR_{40}C(NR_{41})NR_{42}R_{61}$, or $O(CH_2)_{n'}NR_{43}R_{44}$ wherein R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, and R_{61} independently are H or C_{1-3}alkyl, n and n' are 2 or 3; provided one of B and B' is H;

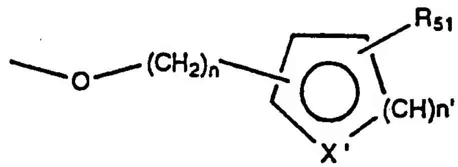
E is



wherein X is CH, N, NH, O, or S; n is 1-3; and n' is 1 or 2;

F, F', and F'' are H, $O(CH_2)_nNR_{45}C(NR_{46})NR_{47}R_{62}$, or $O(CH_2)_{n'}NR_{48}R_{49}$ wherein R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, and R_{62} independently are H or C_{1-3}alkyl, and n and n' are 2 or 3; provided two of F, F', and F'' are H;

G and G' are H, $O(CH_2)_nOR_{50}$, or

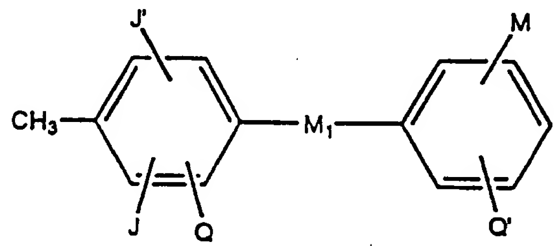


wherein X' is CH, N, NH, O, or S;

R_{50} is H or C_{1-3}alkyl;

R_{51} is H, C_{1-3}alkyl, halogen, OH, or OC_{1-3}alkyl; n is 1-3; and n' is 1 or 2; provided one of G and G' is H.

12. A method of Claim 9 wherein the compounds in the library have the following formula:

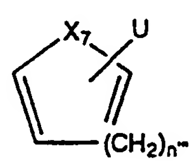


wherein:

M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

J, J', and M independently are $O(CH_2)_nNR_{50}C(NR_{51})NR_{52}R_{65}$ or $O(CH_2)_{n'}NR_{53}R_{54}$ wherein R_{50}, R_{51}, R_{52}, R_{53}, R_{54}, and R_{65} independently are H or C_{1-3}alkyl, and n and n' independently are 2-3;

Q and Q' are H or $O(C_{1-4}$alkyl)T wherein T is C_{1-6}alkyl, CO_2R_{55}, OR_{56}, or



wherein:

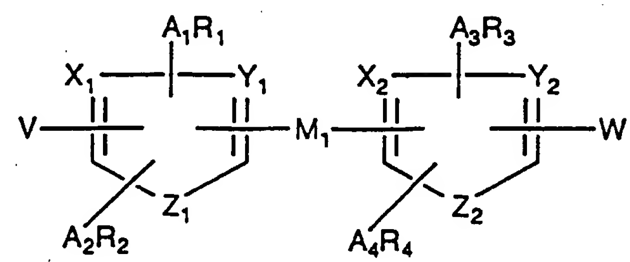
X_7 is CH, N, NH, S, or O;

n''' is 1 or 2;

U is H, C_{1-6}alkyl, halogen, CF_3, or OR_{57}; and

R_{55}, R_{56}, and R_{57} independently are H or C_{1-6}alkyl; provided that Q or Q' is H.

13. A pharmaceutically useful compound having the formula:

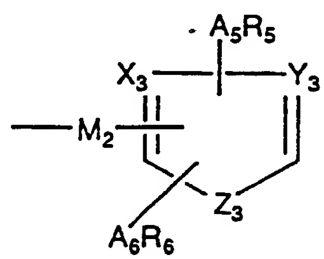


wherein:

X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N. and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

W is H or



X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

M_1 and M_2 independently are a bond or $CR_{84}R_{85}$, $CR_{84}R_{85}CR_{84}R_{85}$, $CR_{84}=CR_{85}$, or $C\equiv C$;

V is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, (C_{0-4}alkyl)$NR_{22}R_{23}$, or (C_{0-4}alkyl)CO_2R_{76};

A_1, A_2, A_3, A_4, A_5, and A_6 independently are absent or present as O, S, NR_{60}; or C_{0-6}alkylC(O)NR_{21}, provided that at least three are present;

R_1, R_2, R_3, R_4, R_5 and R_6 independently are H, C_{0-6}alkylCOR$_{15}$, C_{1-6}alkylR$_{16}$R$_{17}$, C_{1-6}alkylOR$_{24}$ except methoxymethyl, C_{1-6}alkylNR$_{25}$R$_{26}$, C_{0-6}alkylNR$_{80}$C(NR$_{81}$)NR$_{82}$R$_{83}$, C_{1-6}alkylindole, or C_{0-6}alkyl-D;

D is any one or multiple fused saturated or unsaturated five or six membered cyclic hydrocarbon or heterocyclic ring system containing one or more O, N, or S atoms that are unsubstituted or substituted by any accessible combination of 1 to 4 substituents selected from C_{1-6}alkyl, NR$_7$R$_8$, OR$_9$, SR$_{10}$, or COR$_{11}$, halogen, CF_3;

R_7, R_8, R_9, R_{10}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{60}, R_{80}, R_{81}, R_{82}, R_{83}, R_{84} and R_{85} independently are H or C_{1-6}alkyl;

R_{12}, R_{13}, R_{14}, R_{16}, R_{17}, R_{18}, R_{24}, R_{25}, R_{26}, and R_{76} independently are H, C_{1-6}alkyl, phenyl, or substituted phenyl;

R_{11} is OR$_{12}$ or NR$_{13}$R$_{14}$;

R_{15} is OR$_{18}$ or NR$_{19}$R$_{20}$; or

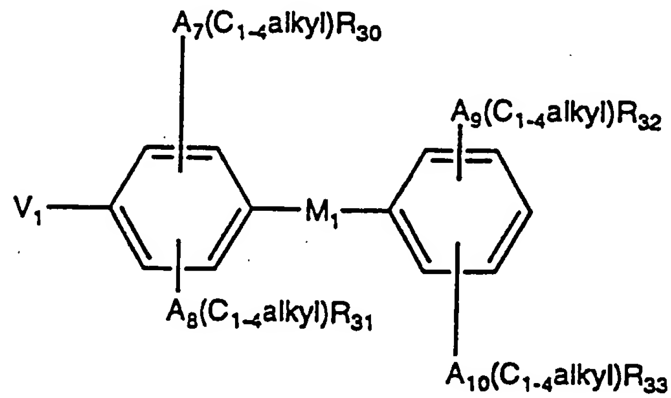
any pharmaceutically useful salt thereof except 2,2',5,5'-(tetrapropynl-1-oxy)biphenyl and salts thereof and compounds wherein at least three of A_1, A_2, A_3, A_4, A_5, and A_6 are oxygen and at least three of R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen, methyl, ethyl, or phenyl and salts thereof.

14. A compound of Claim 13 wherein M_1 is a bond and W is H.

15. A compound of Claim 14 wherein X_1, Y_1, X_2, and Y_2 are CH and Z_1 and Z_2 are CHCH.

16. A compound of Claim 15 wherein A_1, A_2, A_3, A_4, A_5, and A_6 are oxygen.

17. A compound of Claim 13 having the following formula:



wherein:

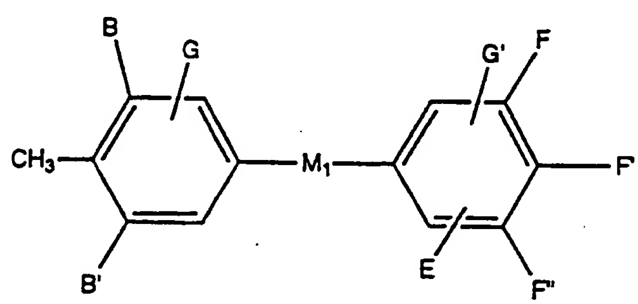
M_1 is a bond or CH_2, CH_2CH_2, $CH=CH$, or $C\equiv C$;

V_1 is H, CH_3, OH or CH_2OH;

A_7, A_8, A_9, and A_{10} independently are absent or present as O provided that three are O; and

R_{30}, R_{31}, R_{32}, and R_{33} independently are OH, NH_2, CO_2H, phenyl, substituted phenyl, $CONH_2$, $NR_{80}C(NR_{81})NR_{82}R_{83}$, C_{1-6}alkyl, imidazole, or indole wherein R_{80} to R_{83} are H or C_{1-4}alkyl.

18. A compound of Claim 13 having the following formula:

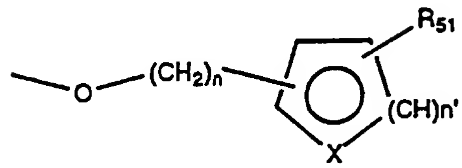


wherein:

M_1 is a bond or CH_2, CH_2CH_2, $CH=CH$, or $C\equiv C$;

B and B' are H, $O(CH_2)_nNR_{40}C(NR_{41})NR_{42}R_{61}$, or $O(CH_2)_{n'}NR_{43}R_{44}$ wherein R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, and R_{61} independently are H or C_{1-3}alkyl, n and n' are 2 or 3; provided one of B and B' is H;

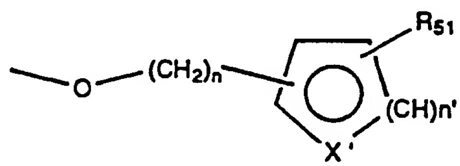
E is



wherein X is CH, N, NH, O, or S; n is 1-3; and n' is 1 or 2;

F, F', and F'' are H, $O(CH_2)_nNR_{45}C(NR_{46})NR_{47}R_{62}$, or $O(CH_2)_{n'}NR_{48}R_{49}$ wherein R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, and R_{62} independently are H or C_{1-3}alkyl, and n and n' are 2 or 3; provided two of F, F', and F'' are H;

G and G' are H, $O(CH_2)_nOR_{50}$, or



wherein X' is CH, N, NH, O, or S;

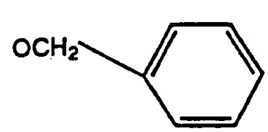
R_{50} is H or C_{1-3}alkyl;

R_{51} is H, C_{1-3}alkyl, halogen, OH, or OC_{1-3}alkyl; n is 1-3; and n' is 1 or 2; provided one of G and G' is H.

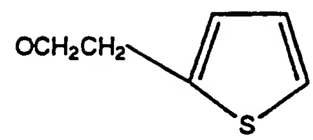
19. A compound of Claim 18 wherein:

B or B' is $OCH_2CH_2NHC(NH)NH_2$;

E is



or

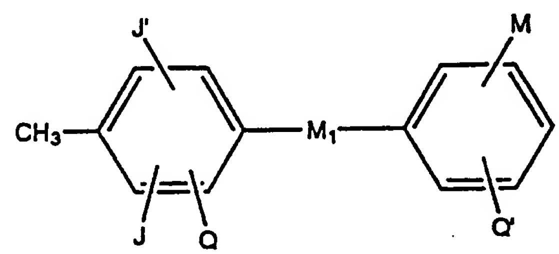


F or F'' are $OCH_2CH_2NHC(NH)NH_2$; and

G and G' are H.

20. A compound of Claim 19 that is 1-methyl-2,5'-diethoxy-guanidino-3'-oxybenzylbiphenyl.

21. A compound of Claim 13 having the following formula:

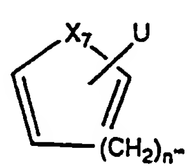


wherein:

M_1 is a bond or CH_2, CH_2CH_2, CH=CH, or C≡C;

J, J', and M independently are $O(CH_2)_nNR_{50}C(NR_{51})NR_{52}R_{65}$ or $O(CH_2)_{n'}NR_{53}R_{54}$ wherein R_{50}, R_{51}, R_{52}, R_{53}, R_{54}, and R_{65} independently are H or C_{1-3}alkyl, and n and n' independently are 2-3;

Q and Q' are H or $O(C_{1-4}alkyl)T$ wherein T is C_{1-6}alkyl, CO_2R_{55}, OR_{56}, or



wherein:

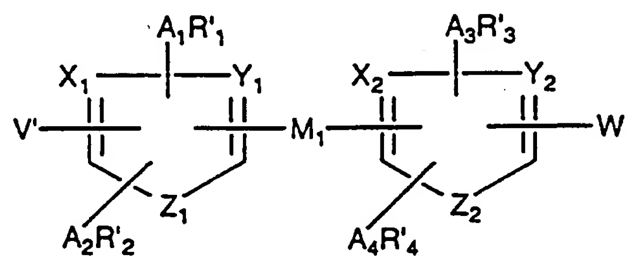
X_7 is CH, N, NH, S, or O;

n''' is 1 or 2;

U is H, C_{1-6}alkyl, halogen, CF_3, or OR_{57}; and

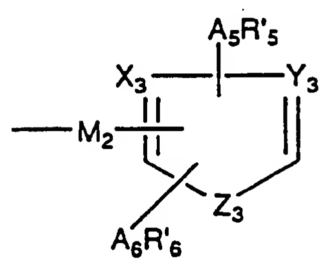
R_{55}, R_{56}, and R_{57} independently are H or C_{1-6}alkyl; provided that Q or Q' is H.

22. A compound having the following formula:



wherein:

W is H or



X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

M_1 and M_2 independently are a bond or $CR_{84}R_{85}$, $CR_{84}R_{85}CR_{84}R_{85}$, $CR_{84}=CR_{85}$, or $C\equiv C$;

V' is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, (C_{0-4}alkyl)$NR_{22}R_{23}$, or (C_{0-4}alkyl)CO_2R_{76} or a bond to a solid support;

A_1, A_2, A_3, A_4, A_5, and A_6 independently are absent or present as O, S, NR_{60}; or C_{0-6}alkylC(O)NR_{21}, provided that at least three are present;

R'_1, R'_2, R'_3, R'_4, R'_5 and R'_6 independently are a protecting group or H, C_{0-6}alkylCOR_{15}, C_{1-6}alkyl$R_{16}R_{17}$, C_{1-6}alkylOR_{24} except methoxymethyl, C_{1-6}alkyl$NR_{25}R_{26}$, C_{0-6}alkyl$NR_{80}C(NR_{81})NR_{82}R_{83}$, C_{1-6}alkylindole, or C_{0-6}alkyl-D, provided that at least one of R'_1 to R'_6 is a protecting group;

D is any one or multiple fused saturated or unsaturated five or six membered cyclic hydrocarbon or heterocyclic ring system containing one or more O, N, or S atoms that are unsubstituted or substituted by any accessible combination of 1 to 4 substituents selected from C_{1-6}alkyl, NR_7R_8, OR_9, SR_{10}, or COR_{11}, halogen, CF_3;

R_7, R_8, R_9, R_{10}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{60}, R_{80}, R_{81}, R_{82}, R_{83}, R_{84} and R_{85} independently are H or C_{1-6}alkyl;

R_{12}, R_{13}, R_{14}, R_{16}, R_{17}, R_{18}, R_{24}, R_{25}, R_{26}, and R_{76} independently are H, C_{1-6}alkyl, phenyl, or substituted phenyl;

R_{11} is OR_{12} or $NR_{13}R_{14}$; or

R_{15} is OR_{18} or $NR_{19}R_{20}$.

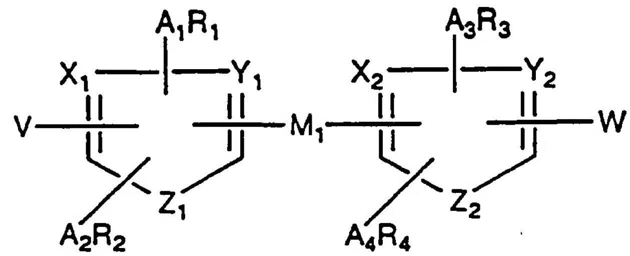
23. A compound of Claim 22 wherein X_1, Y_1, X_2, Y_2, X_3, and Y_3 are CH and Z_1, Z_2, and Z_3 are CHCH.

24. A compound of Claim 23 wherein A_1, A_2, A_3, A_4, A_5, and A_6 are oxygen.

25. A compound of Claim 22 wherein X_1, Y_1, X_2, Y_2 are CH, Z_1 and Z_2 are CHCH, and W is H or C_{1-6}alkyl.

26. A compound of Claim 25 wherein A_1, A_2, A_3, and A_4 are oxygen.

27. A method of preparing a compound of the following formula:

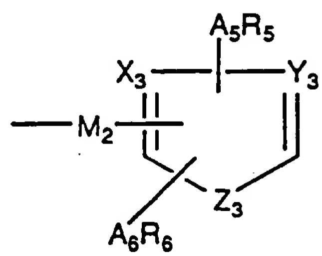


wherein:

X_1, Y_1 and Z_1 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

X_2, Y_2, and Z_2 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

W is H or



X_3, Y_3 and Z_3 are any accessible combination of CH, CHCH, O, S, N, and NH provided that at least one is CH or CHCH and not more than one is CHCH;

M_1 and M_2 independently are a bond or $CR_{84}R_{85}$, $CR_{84}R_{85}CR_{84}R_{85}$, $CR_{84}=CR_{85}$, or $C\equiv C$;

V is H, C_{1-6}alkyl, halo, (C_{0-4}alkyl)OH, (C_{0-4}alkyl)SH, (C_{0-4}alkyl)$NR_{22}R_{23}$, or (C_{0-4}alkyl)CO_2R_{76};

A_1, A_2, A_3, A_4, A_5, and A_6 independently are absent or present as O, S, NR_{60}; or C_{0-6}alkylC(O)NR_{21}, provided that at least three are present;

R_1, R_2, R_3, R_4, R_5 and R_6 independently are H, C_{0-6}alkylCOR$_{15}$, C_{1-6}alkylR$_{16}$R$_{17}$, C_{1-6}alkylOR$_{24}$ except methoxymethyl, C_{1-6}alkylNR$_{25}$R$_{26}$, C_{0-6}alkylNR$_{80}$C(NR$_{81}$)NR$_{82}$R$_{83}$, C_{1-6}alkylindole, or C_{0-6}alkyl-D;

D is any one or multiple fused saturated or unsaturated five or six membered cyclic hydrocarbon or heterocyclic ring system containing one or more O, N, or S atoms that are unsubstituted or substituted by any accessible combination of 1 to 4 substituents selected from C_{1-6}alkyl, NR$_7$R$_8$, OR$_9$, SR$_{10}$, or COR$_{11}$, halogen, CF_3;

R_7, R_8, R_9, R_{10}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{60}, R_{80}, R_{81}, R_{82}, R_{83}, R_{84} and R_{85} independently are H or C_{1-6}alkyl;

R_{12}, R_{13}, R_{14}, R_{16}, R_{17}, R_{18}, R_{24}, R_{25}, R_{26}, and R_{76} independently are H, C_{1-6}alkyl, phenyl, or substituted phenyl;

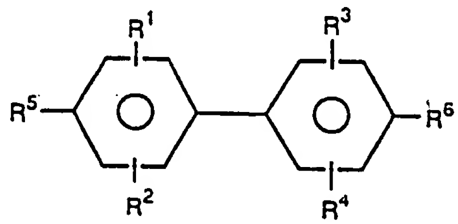
R_{11} is OR$_{12}$ or NR$_{13}$R$_{14}$;

R_{15} is OR$_{18}$ or NR$_{19}$R$_{20}$; or

any pharmaceutically useful salt thereof that comprises cleaving from a solid support a compound of the above formula that is bound to the solid support through the V substituent.

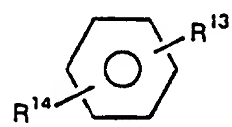
AMENDED CLAIMS
[received by the International Bureau on 5 December 1994 (05.12.94);
original claims 1-27 replaced by amended claims 1-6 (4 pages)]

1. A process for sequentially preparing a universal library of compounds which all have the general formula:



(I)

wherein R^1, R^2, R^3, R^4, R^{13} and R^{14} are each individually OR^7, SR^8, NR^9R^{10}, C_1-C_6 alkyl-C(O)$NR^{11}R^{12}$, or CN;

R^6 is hydrogen, or  ;

R^5 is hydrogen, phenyl or substituted phenyl;

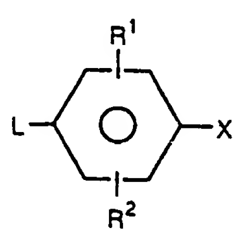
R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkyl-CO_2R^{15}, aryl, arylalkyl, C_1-C_6 alkyl-OR^{16} except methoxy, C_1-C_6 alkyl-$NR^{17}R^{18}$, C_1-C_6 alkyl-NHC(NH)NH_2, or C_1-C_6 alkyl-substituted heterocycle;

R^{15}, R^{16}, R^{17} and R^{18} are each individually hydrogen or C_1-C_6 alkyl;

comprising the steps of:

a) providing a solid phase support with a cleavable linker coupled thereto;

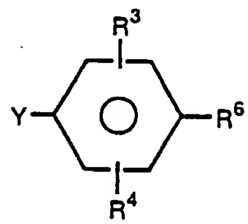
b) preparing a first scaffold of the general formula:



wherein L is a moiety which can be bonded to said cleavable linker, and X is a moiety which can facilitate covalent bonding to a second scaffold;

c) coupling said first scaffold to said linker;

d) preparing a second scaffold of the general formula;

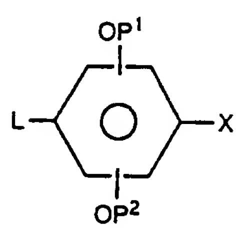


wherein Y is a moiety which reacts with X to allow covalent bonding of the first and second scaffolds;

e) coupling said first and second scaffolds to form the Formula I compounds attached to said linker; and

f) cleaving said Formula I compounds from said linker.

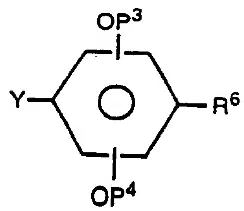
2. The process of Claim 1 wherein step (b) includes providing a base compound of the general formula:



wherein P^1 and P^2 are protecting groups; and

step (c) includes removing said protecting groups and substituting with functional groups to form the first scaffold after coupling the base compound to the linker but prior to step (c).

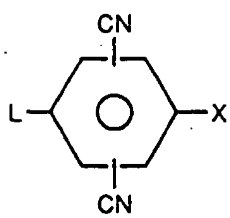
3. The process of Claim 2 wherein step (d) includes providing a second base compound of the formula:



wherein P^3 and P^4 are protecting groups; and

step (e) includes removing said protecting groups and substituting with functional groups to form the second scaffold after coupling the first scaffold and the second base compound and prior to step (f).

4. The process of Claim 1 wherein step (b) includes providing a base compound of the formula:

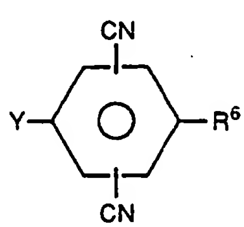


;

hydrolyzing the nitrile moieties to carboxyl moieties; and

reacting the base compound with an amine to produce the first scaffold where R^1 and R^2 are each $C(O)NR^{11}R^{12}$.

5. The process of Claim 4 wherein step (d) includes providing a second base compound of the formula:



hydrolyzing the nitrile moieties to carboxyl moieties; and

reacting the second base compound with an amine to produce the second scaffold where R^3 and R^4 are each $C(O)NR^{11}R^{12}$.

6. The process of Claim 1 wherein said solid phase support is a Merrifield resin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07780

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :G01N 33/53, 33/543; A61K 31/00
US CL :435/7.1; 436/518; 514/155, 183
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1; 436/518; 514/155, 183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, APS
search terms: structure search, phenyl, benzene, biological activity, assay

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, VOLUME 114, ISSUED 1992, BUNIN ET AL. "A General and Expedient Method for the Solid-Phase Synthesis of 1,4-Benzodiazepine Derivatives", pages 10997-10998, see entire article.	1,2,4
X --- Y	AUSTRALIAN JOURNAL OF CHEMISTRY, VOLUME 45, ISSUED 1992, BANWELL ET AL., "Synthesis and Tubilin-Binding Properties of Some AC- and ABC-Analogues of Allocolchicine", pages 1967-1982, see pages 1968, 1969.	1,2,4-8 ----------- 3,9,10,13-17,22-27
P,X --- Y	US, A, 5,250,548 (WINN ET AL.) 05 OCTOBER 1993, see column 2, line 15-column 6, line 64 and column 87, line 1-column 189, line 65.	1, 2, 4-8 ------------- 11,12,18- 21

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 SEPTEMBER 1994	03 OCT 1994

Name and mailing address of the ISA/US	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07780

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,218,124 (FAILLI ET AL.) 08 JUNE 1993, SEE COLUMN 3, LINE 56-COLUMN 6, LINE 28.	1-27